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APPLICATION TRANSMITTAL LETTER

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Transmitted herewith for filing is the patent application of Doris COIT, Angelica MEDINA-SELBY,
Mark SELBY and Michael HOUGHTON for NOVEL HCV NON-STRUCTURAL POLYPEPTIDE,
claiming priority to provisional application serial no. 60/167,502, filed November 24, 1999.

Enclosed are:

- 100 sheets of drawings.
- ☐ A claim for foreign priority under 35 U.S.C. § 119/363 in
☐ a separate document ☐ the declaration.
- ☒ A claim for priority under 35 U.S.C. § 119(e)(1) in
☐ a separate document ☒ the declaration.
- ☐ A certified copy of the priority document.
- ☐ Verified Statement(s) Claiming Small Entity Status.
- ☒ Other: Sequence Listing (pp. 1-183); diskette; Statement to Support Filing and
Submission in Accordance with 37 C.F.R. §§ 1.821-1.825; Title page; return receipt
postcard.

The declaration of the inventor ☒ is enclosed ☒ unsigned.

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The fee has been calculated as follows:

A. Basic Application Fee		\$710
B. Total Claims $42 - 20 = 22$	x \$18	396
C. Independent Claims $2 - 3 = 0$	x \$80	0
D. If multiple dependent claims present, add	\$270	0
E. Total Application Fee (Total of A, B, C, & D)	=	<u>1106</u>
F. If small entity status is claimed, reduce Total Application Fee by 50%		0
G. Application Fee Due (E - F)	=	<u>1106</u>
H. Assignment Recording Fee of \$40.00 if assignment document is enclosed	\$40	<u>NA</u>
I. TOTAL FEE (G + H)		\$1106

Respectfully submitted,

Date: Nov 22, 2000

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Application for U.S. Letters Patent Entitled

NOVEL HCV NON-STRUCTURAL POLYPEPTIDE

claiming priority to provisional application serial no. 60/167,502, filed November 24, 1999

by Inventors:

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5 **NOVEL HCV NON-STRUCTURAL POLYPEPTIDE****CROSS-REFERENCE TO RELATED APPLICATION**

 This application is related to provisional patent application serial no. 60/167,502,
filed November 24, 1999 from which priority is claimed under 35 USC §119(e)(1) and
10 which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

 The present invention relates to polypeptides comprising a mutant non-structural
Hepatitis C virus ("HCV") polypeptide useful for immunogenic compounds for use against
15 HCV, methods of preparing and using the same, and immunogenic compositions
comprising the same. The present invention also relates to compositions comprising (a) a
mutant non-structural HCV polypeptide and (b) a viral polypeptide that is not a non-
structural HCV polypeptide and methods of using these compositions.

20 **BACKGROUND OF THE INVENTION**

 HCV is now recognized as the major agent of chronic hepatitis and liver disease
worldwide. It is estimated that HCV infects about 400 million people worldwide,
corresponding to more than 3% of the world population.

 Hepatitis C virus ("HCV") is a small enveloped RNA *flavivirus*, which contains a
25 positive-stranded RNA genome of about 10 kilobases. The genome has a single
uninterrupted ORF that encodes a protein of 3010-3011 amino acids. The structural
proteins of HCV include a core protein (C), which is highly immunogenic, as well as two
envelope proteins (E1 and E2), which likely form a heterodimer *in vivo*, and non-structural
proteins NS2-NS5. It is known that the NS3 region of the virus is important for post-
30 translational processing of the polyprotein into individual proteins, and the NS5 region
encodes an RNA-dependant RNA polymerase.

Virus-specific T lymphocytes, along with neutralizing antibodies, are the mainstay of the antiviral immune defense in established viral infections. Whereas CD8⁺ cytotoxic T cells eliminate virus-infected-cells, CD4⁺ T helper cells are essential for the efficient regulation of the antiviral immune response. CD4⁺ T helper cells recognize specific antigens as peptides bound to autologous HLA class II molecules (viral antigens or particles are taken up by professional antigen-presenting cells, processed to peptides, bound to HLA class II molecules in the lysosomal compartment, and transported back to the cell surface). Several observations support an important role of CD4⁺ T cells in the elimination of HCV infection. Tsai *et al.*, 1997 Hepatology 25:449-458; Diepolder et al 1995 Lancet 346: 1—6-1009; Missale et al 1996 JCI 98: 706-714; Botarelli et al 1993; Gastro 104: 580-587; Diepolder et al 1997 J.Virol 71: 6011. Immunogenic peptides usually have a minimal length of 8-11 amino acids. However, since the peptide binding groove of HLA class II molecules seems to be open at both ends, longer peptides are tolerated. Thus peptides eluted from HLA class II molecules are typically in the range of 15-25 amino acids. HLA class II molecules are extremely polymorphic and each allele seems to have its individual requirements for peptide binding. Thus the HLA class II repertoire of a given individual determines which viral peptides can be presented to T cells. Recognition of the specific HLA-peptide complex by the T cell receptor accompanied by appropriate costimulatory signals lead to T cell activation, secretion of cytokines, and T cell proliferation.

Numerous studies demonstrate that HLA Class II restricted CD4⁺ responses are determined by stimulating peripheral blood mononuclear cells with recombinant viral antigens or peptides. Botarelli *et al.*, (1993) Gastroenterology 104:580-587; Farrari *et al.*, (1994) Hepatology 19:286-295; Minutello *et al.*, (1993) C. J. Exp. Med. 178:17-25; Hoffmann *et al.*, (1995) Hepatology 21:632-638; Iwata *et al.*, (1995) Hepatology 22:1057-1064; and Tsai *et al.*, (1995) Hepatology 21:908-912.

Polyclonal multispecific CD8⁺ T cell responses have been detected in patients with chronic hepatitis C. Additionally, CD8⁺ CTL's were shown to be important in resolving acute HCV infection in chimpanzees (Cooper *et al.*, Immunity 1999). About 50% of patients with chronic hepatitis C demonstrate a detectable virus-specific CD4⁺ T cell

response, which is most frequently directed against HCV core and/or NS4 and tends to be more common in patients who achieve sustained viral clearance during interferon- α therapy.

Depending on the pattern of lymphokines, CD4⁺ T helper cells have been classified as TH1, TH0, or TH2. Cytokines of the TH1 type are typically IFN- γ , lymphotoxin, and interleukin-2 (IL-2), which are believed to support activation of virus-specific CD8⁺ T cells and natural killer cells. The TH2 cytokines IL-4, IL-5, IL-10, and IL-13 are important for B cell activation and differentiation, thus inducing a humoral immune response.

During acute hepatitis C infection a strong and sustained TH1/TH0 response to NS3 and possibly to other nonstructural proteins is associated with a self-limited course of the disease. Diapolder *et al.*, (1995) Lancet 346:1006-1007, showed all CD4⁺ T cell clones to have a TH1 or TH0 cytokine profile, suggesting that the clones support cytotoxic immune mechanisms *in vivo*. The majority of CD4⁺ T cell clones responded to a relatively short segment of NS3, namely amino acids 1207-1278, suggesting that this region of NS3 is immunodominant for CD4⁺ T cells. More than 70% of those who contract HCV develop chronic infection and hepatitis, and a significant portion of them progress to cirrhosis and eventually hepatocellular carcinoma. The only approved therapy at present is a 6- to 12- month course of interferon α , which leads to sustained improvement in only 20% of patients. So far, no commercial vaccine is available.

Thus, there remains a need for compositions and methods capable of promoting anti-HCV responses.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to isolated polypeptides comprising mutant hepatitis C ("HCV") polypeptides comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, NS3 is encoded by a nucleic acid sequence having an N-terminal deletion to remove the catalytic domain. The NS mutant polypeptides can include NS3, NS4s, NS4b, NS5a, NS5b or portions thereof. For example, in various embodiments, the mutant NS polypeptide comprises NS3, NS4 (NS4a and NS4b) and NS5 (NS5a and NS5b). In other embodiments, the NS polypeptide consists of NS3 and NS4 (for example,

NS4a and/or NS4b) or NS3 and NS5 (for example, NS5a and/or NS5b). Other combinations of full-length or fragments of non-structural components are also contemplated.

In another preferred aspect, the polypeptides further comprise a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. Thus, the invention includes an isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3 that functionally disrupts the catalytic domain. The mutation can be, for example, a deletion or a substitution mutation. In certain embodiments, the mutant NS polypeptide comprises NS3, NS4 and NS5. In other embodiments, the mutant NS polypeptides described herein further comprise a second viral polypeptide that is not NS3, NS4, or NS5 of HCV, for example an HCV Core polypeptide ("C"), or fragment thereof, or an HCV envelope protein ("E"), for example E1 and/or E2. In certain embodiments, C is truncated (*e.g.*, at amino acid 121).

In another aspect, the present invention relates to compositions comprising any of the mutant hepatitis C ("HCV") polypeptides described herein, for example polypeptides comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, NS3 is encoded by a nucleic acid sequence having an N-terminal deletion to disrupt the function of the catalytic domain, for example by removing this domain. In another preferred aspect, the polypeptides further comprise a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another aspect, the invention includes a composition

comprising (a) any of the polypeptides described herein; and (b) a pharmaceutically acceptable excipient (*e.g.*, carrier and/or adjuvant).

In another aspect, the invention includes an isolated and purified polynucleotide which encodes any of the mutant HCV polypeptides described herein. In certain
5 embodiments, the invention includes a composition comprising (a) the isolated purified polynucleotide encoding any of the mutant HCV polypeptides; and (b) a pharmaceutically acceptable excipient. The polynucleotide, can be for example, DNA in a plasmid, or is in a plasmid. Additionally, the polynucleotides described herein may be included in an expression vector as shown in the attached Figures and Sequence Listings.

10 In another aspect, the present invention relates to host cells transformed with expression vectors comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising at least portions of NS3, NS4, and NS5. In a preferred aspect, the expression vectors of the host cells further comprises at least one nucleic acid sequence encoding a viral polypeptide that is not a non-structural HCV polypeptide. Such
15 polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In
20 another preferred aspect the nucleic acid sequences of the expression vectors are coexpressed. In yet another preferred aspect, the host cells are yeast cells or mammalian cells.

In another aspect, the present invention relates to expression vectors comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising NS3, NS4, and
25 NS5. In a preferred aspect, the expression vectors of the host cells further comprises at least one nucleic acid sequence encoding a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Importantly, such polypeptides
30 need not be encoded by a natural HCV genome, such as, for example, truncated or

otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another aspect, the present invention relates to methods of preparing a mutant HCV polypeptides. In a preferred aspect, the method comprises the steps of transforming a host cell with an expression vector, said vector comprising a nucleic acid sequence encoding a mutant HCV polypeptide comprising at least portions of NS3, NS4, and NS5, and isolating said polypeptide. In another preferred aspect the HCV polypeptide further comprises a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, and include, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, such as, for example, polypeptides of HBV. In another preferred aspect the host cells are yeast cells or mammalian cells.

In another aspect, the present invention relates to antibodies which specifically bind to mutant HCV polypeptide comprising NS3, NS4, and NS5, and to methods of making and using the same. In a preferred aspect, the HCV polypeptide further comprises a viral polypeptide that is not a non-structural HCV polypeptide. Such polypeptides are preferably C, or antigenic fragments thereof, more preferably, truncated C of HCV. Other polypeptides are preferably E, or antigenic fragments thereof, more preferably, E1 or E2 of HCV. Such polypeptides need not be encoded by a natural HCV genome, such as, for example, truncated or otherwise mutant HCV polypeptides or polypeptides derived from other genomes, and include, for example, polypeptides of HBV. In another preferred aspect, the antibody is either monoclonal or polyclonal.

In yet another aspect, a method of preparing a mutant NS HCV polypeptide, wherein the method comprises the steps of (a) transforming a host cell with any of the expression vectors described herein, under conditions wherein the polypeptide is expressed; and (b) isolating the polypeptide. The host cell can be, for example, a yeast cell, a mammalian cell a plant cell or an insect cell. The polypeptide can be expressed and isolated intracellularly or can be secreted and isolated from the surrounding environment.

In a still further aspect, a method of eliciting an immune response in a subject is provided. The immune response can be elicited by administering any of the polynucleotides and/or polypeptides described herein in one or multiple doses.

These and other embodiments of the subject invention will readily occur to those of skill in the art in light of the disclosure herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the cloning scheme for generating pCMV-NS35.

FIG. 2 shows the 9621bp vector pCMV-NS35.

FIG. 3 shows the nucleic acid sequence of pCMV-NS35 (SEQ ID NO:1), including the nucleic acid sequence of the NS35 ORF, and also the translation of NS35 (SEQ ID NO:2).

FIG. 4 shows the 9621bp pCMV-delNS35.

FIG. 5 shows the nucleic acid sequence of pCMV-delNS35 (SEQ ID NO:3), including the nucleic acid sequence of the delNS35 ORF, and also the translation of the delNS35 polypeptide (SEQ ID NO:4).

FIG. 6 shows the 4276bp pCMV-II.

FIG. 7 shows the nucleic acid sequence of pCMV-II (SEQ ID NO:5).

FIG. 8 shows the 6300bp pCMV-NS34A.

FIG. 9 shows the nucleic acid sequence of pCMV-NS34A (SEQ ID NO:6), including the nucleic acid sequence of the NS34A ORF, and also the translation of NS34A (SEQ ID NO:7).

FIG. 10 shows the cloning scheme for generating pd.ΔNS3NS5.

FIG. 11 shows the nucleic and amino acid sequences of pd.ΔNS3NS5 (SEQ ID NO:8 and 9).

FIG. 12 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.

FIG. 13 shows the cloning scheme for generating pd.ΔNS3NS5.pj.

FIG. 14 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj (SEQ ID NO:10 and 11).

FIG. 15 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of ΔNS3NS5 polypeptide.

FIG. 16 shows the cloning scheme for generating pdΔNS3NS5.pj.core121RT and

5 pdΔNS3NS5.pj.core173RT.

FIG. 17 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core121 (SEQ ID NO:12 and 13).

FIG. 18 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core173 (SEQ ID NO:14 and 15).

10 FIG. 19 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of ΔNS3NS5.core121 and ΔNS3NS5.core173 polypeptides. Lanes 1 and 7 show See Blue Standards. Lane 2 shows control yeast plasmid. Lanes 3 and 4 show ΔNS3NS5.core121RT polypeptide, colonies 1 and 2. Lanes 5 and 6 show
15 ΔNS3NS5.core173RT polypeptide, colonies 3 and 4.

FIG. 20 shows the cloning scheme for generating pdΔNS3NS5.pj.core140RT and pdΔNS3NS5.pj.core150RT.

FIG. 21 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core140 (SEQ ID NO:16 and 17).

20 FIG. 22 shows the nucleic and amino acid sequences of pd.ΔNS3NS5.pj.core150 (SEQ ID NO:18 and 19).

FIG. 23 shows the Western blot of proteins expressed by *S. cerevisiae* strain AD3 transformed with pd.ΔNS3NS5.pj, specifically demonstrating the expression of ΔNS3NS5core140 and ΔNS3NS5core150 polypeptides. Lane 1 shows See Blue

25 Standards. Lanes 2 and 3 show ΔNS3NS5core140RT polypeptide, colonies 5 and 6. Lanes 4 and 5 show ΔNS3NS5core150RT polypeptide, colonies 7 and 8. Lane 6 shows control yeast plasmid. Lane 7 shows ΔNS3NS5core121RT polypeptide, colony 1. Lane 8 shows ΔNS3NS5core173RT polypeptide, colony 5.

DETAILED DESCRIPTION OF THE INVENTION

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology, microbiology, recombinant DNA techniques, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See e.g., Sambrook, et al., MOLECULAR CLONING; A LABORATORY MANUAL (1989); DNA CLONING, VOLUMES I AND II (D. N. Glover ed. 1985); OLIGONUCLEOTIDE SYNTHESIS (M. J. Gait ed., 1984); NUCLEIC ACID HYBRIDIZATION (B. D. Hames & S. J. Higgins eds. 1984); TRANSCRIPTION AND TRANSLATION (B. D. Hames & S. J. Higgins eds. 1984); ANIMAL CELL CULTURE (R. I. Freshney ed. 1986); IMMOBILIZED CELLS AND ENZYMES (IRL Press, 1986); B. Perbal, A PRACTICAL GUIDE TO MOLECULAR CLONING (1984); the series, METHODS OF ENZYMOLOGY (Academic Press, Inc.); GENE TRANSFER VECTORS FOR MAMMALIAN CELLS (J. H. Miller and M. P. Calos eds. 1987, Cold Springs Harbor Laboratory), Methods in Enzymology Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively); Mayer and Walker eds. (1987), IMMUNOHISTOCHEMICAL METHODS IN CELL AND MOLECULAR BIOLOGY (Academic Press, London); Scopes, (1987), PROTEIN PURIFICATION: PRINCIPALS AND PRACTICE, Second Edition (Springer-Verlag, New York); and HANDBOOK OF EXPERIMENTAL IMMUNOLOGY, VOLUMES I-IV (D. M. Weir and C. C. Blackwell eds. 1986).

All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entirety.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to "an antigen" includes a mixture of two or more antigens, and the like.

I. Definitions

In describing the present invention, the following terms will be employed, and are intended to be defined as indicated below.

The term "hepatitis C virus" (HCV) refers to an agent causative of Non-A, Non-B Hepatitis (NANBH). The nucleic acid sequence and putative amino acid sequence of HCV is described in U.S. Patent Nos. 5,856,437 and 5,350,671. The disease caused by HCV is called hepatitis C, formerly called NANBH. The term HCV, as used herein, denotes a viral species of which pathenogenic strains cause NANBH, as well as attenuated strains or defective interfering particles derived therefrom.

HCV is a member of the viral family flaviviridae. The morphology and composition of Flavivirus particles are known, and are discussed in Reed et al., *Curr. Stud. Hematol. Blood Transfus.* (1998), 62:1-37; HEPATITIS C VIRUSES IN FIELDS VIROLOGY (B.N. Fields, D.M. Knipe, P.M. Howley, eds.) (3d ed. 1996). It has recently been found that portions of the HCV genome are also homologous to pestiviruses.

Generally, with respect to morphology, Flaviviruses contain a central nucleocapsid surrounded by a lipid bilayer. Virions are spherical and have a diameter of about 40-50 nm. Their cores are about 25-30 nm in diameter. Along the outer surface of the virion envelope are projections that are about 5-10 nm long with terminal knobs about 2 nm in diameter.

The HCV genome is comprised of RNA. It is known that RNA containing viruses have relatively high rates of spontaneous mutation. Therefore, there can be multiple strains, which can be virulent or avirulent, within the HCV class or species. The ORF of HCV, including the translation spans of the core, non-structural, and envelope proteins, is shown in U.S. Patent Nos. 5,856,437 and 5,350,671.

The terms "polypeptide" and "protein" refer to a polymer of amino acid residues and are not limited to a minimum length of the product. Thus, peptides, oligopeptides, dimers, multimers, and the like, are included within the definition. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include postexpression modifications of the polypeptide, for example, glycosylation, acetylation, phosphorylation and the like. Furthermore, for purposes of the present invention, a

“polypeptide” refers to a protein which includes modifications, such as deletions, additions and substitutions (generally conservative in nature), to the native sequence, so long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

An HCV polypeptide is a polypeptide, as defined above, derived from the HCV polyprotein. The polypeptide need not be physically derived from HCV, but may be synthetically or recombinantly produced. Moreover, the polypeptide may be derived from any of the various HCV strains, such as from strains 1, 2, 3 or 4 of HCV. A number of conserved and variable regions are known between these strains and, in general, the amino acid sequences of epitopes derived from these regions will have a high degree of sequence homology, e.g., amino acid sequence homology of more than 30%, preferably more than 40%, when the two sequences are aligned and homology determined by any of the programs or algorithms described herein. Thus, for example, the term “NS4” polypeptide refers to native NS4 from any of the various HCV strains, as well as NS4 analogs, muteins and immunogenic fragments, as defined further below.

Further, the terms “ΔNS35,” “delNS35,” “ΔNS3NS5,” and “ΔNS3-5” as used herein refer to a mutant polypeptide, comprising at least portions of NS3, NS4, or NS5, comprising a deletion in, or mutation of, the NS3 protease active site region to render the protease non-functional. In one embodiment, ΔNS3-5 comprises amino acids 1242-3011, as shown in FIG. 5, or polypeptides substantially homologous thereto. It will be readily apparent to one of ordinary skill in the art how to determine that NS3 protease has been rendered non-functional. If the protease is functional, one will obtain protein of the expected molecular weight upon expression. As set forth in Example 2 and Figure 15, using SDS-page, 4-20%, a protein having a molecular weight of approximately 194kD was obtained when strain AD3 was transformed with pd.ΔNS3NS5.PJ clone #5. One skilled in the art could readily determine whether a protein of the desired molecular weight was expressed for any given deletion or mutation.

The terms “analog” and “mutein” refer to biologically active derivatives of the reference molecule, or fragments of such derivatives, that retain desired activity, such as

the ability to stimulate a cell-mediated immune response, as defined below. In general, the term "analog" refers to compounds having a native polypeptide sequence and structure with one or more amino acid additions, substitutions (generally conservative in nature) and/or deletions, relative to the native molecule, so long as the modifications do not
5 destroy immunogenic activity. The term "mutein" refers to peptides having one or more peptide mimics ("peptoids"), such as those described in International Publication No. WO 91/04282. Preferably, the analog or mutein has at least the same immunoactivity as the native molecule. Methods for making polypeptide analogs and muteins are known in the art and are described further below.

10 Particularly preferred analogs include substitutions that are conservative in nature, i.e., those substitutions that take place within a family of amino acids that are related in their side chains. Specifically, amino acids are generally divided into four families: (1) acidic -- aspartate and glutamate; (2) basic -- lysine, arginine, histidine; (3) non-polar -- alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4)
15 uncharged polar -- glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. Phenylalanine, tryptophan, and tyrosine are sometimes classified as aromatic amino acids. For example, it is reasonably predictable that an isolated replacement of leucine with isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar conservative replacement of an amino acid with a structurally related amino acid, will not
20 have a major effect on the biological activity. For example, the polypeptide of interest may include up to about 5-10 conservative or non-conservative amino acid substitutions, or even up to about 15-25 conservative or non-conservative amino acid substitutions, or any integer between 5-25, so long as the desired function of the molecule remains intact. One of skill in the art may readily determine regions of the molecule of interest that can tolerate
25 change by reference to Hopp/Woods and Kyte-Doolittle plots, well known in the art.

By "fragment" is intended a polypeptide consisting of only a part of the intact full-length polypeptide sequence and structure. The fragment can include a C-terminal deletion and/or an N-terminal deletion of the native polypeptide. An "immunogenic fragment" of a particular HCV protein will generally include at least about 5-10 contiguous amino acid
30 residues of the full-length molecule, preferably at least about 15-25 contiguous amino acid

residues of the full-length molecule, and most preferably at least about 20-50 or more contiguous amino acid residues of the full-length molecule, that define an epitope, or any integer between 5 amino acids and the full-length sequence, provided that the fragment in question retains immunogenic activity, as measured by the assays described herein. For a description of various HCV epitopes, see, e.g., Chien et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:10011-10015; Chien et al., *J. Gastroent. Hepatol.* (1993) 8:S33-39; Chien et al., International Publication No. WO 93/00365; Chien, D.Y., International Publication No. WO 94/01778; commonly owned, allowed U.S. Patent Application Serial Nos. 08/403,590 and 08/444,818.

The term "epitope" as used herein refers to a sequence of at least about 3 to 5, preferably about 5 to 10 or 15, and not more than about 1,000 amino acids (or any integer therebetween), which define a sequence that by itself or as part of a larger sequence, binds to an antibody generated in response to such sequence. There is no critical upper limit to the length of the fragment, which may comprise nearly the full-length of the protein sequence, or even a fusion protein comprising two or more epitopes from the HCV polyprotein. An epitope for use in the subject invention is not limited to a polypeptide having the exact sequence of the portion of the parent protein from which it is derived. Indeed, viral genomes are in a state of constant flux and contain several variable domains which exhibit relatively high degrees of variability between isolates. Thus the term "epitope" encompasses sequences identical to the native sequence, as well as modifications to the native sequence, such as deletions, additions and substitutions (generally conservative in nature).

Regions of a given polypeptide that include an epitope can be identified using any number of epitope mapping techniques, well known in the art. See, e.g., *Epitope Mapping Protocols* in *Methods in Molecular Biology*, Vol. 66 (Glenn E. Morris, Ed., 1996) Humana Press, Totowa, New Jersey. For example, linear epitopes may be determined by e.g., concurrently synthesizing large numbers of peptides on solid supports, the peptides corresponding to portions of the protein molecule, and reacting the peptides with antibodies while the peptides are still attached to the supports. Such techniques are known in the art and described in, e.g., U.S. Patent No. 4,708,871; Geysen et al. (1984) *Proc.*

Natl. Acad. Sci. USA 81:3998-4002; Geysen et al. (1986) *Molec. Immunol.* 23:709-715, all incorporated herein by reference in their entirety. Similarly, conformational epitopes are readily identified by determining spatial conformation of amino acids such as by, e.g., x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., *Epitope Mapping Protocols, supra*. Antigenic regions of proteins can also be identified using standard antigenicity and hydropathy plots, such as those calculated using, e.g., the Omega version 1.0 software program available from the Oxford Molecular Group. This computer program employs the Hopp/Woods method, Hopp et al., *Proc. Natl. Acad. Sci USA* (1981) 78:3824-3828 for determining antigenicity profiles, and the Kyte-Doolittle technique, Kyte et al., *J. Mol. Biol.* (1982) 157:105-132 for hydropathy plots.

As used herein, the term "conformational epitope" refers to a portion of a full-length protein, or an analog or mutein thereof, having structural features native to the amino acid sequence encoding the epitope within the full-length natural protein. Native structural features include, but are not limited to, glycosylation and three dimensional structure. Preferably, a conformational epitope is produced recombinantly and is expressed in a cell from which it is extractable under conditions which preserve its desired structural features, e.g. without denaturation of the epitope. Such cells include bacteria, yeast, insect, and mammalian cells. Expression and isolation of recombinant conformational epitopes from the HCV polyprotein are described in e.g., International Publication Nos. WO 96/04301, WO 94/01778, WO 95/33053, WO 92/08734, which applications are herein incorporated by reference in their entirety.

An "immunological response" to an HCV antigen (including both polypeptide and polynucleotides encoding polypeptides that are expressed *in vivo*) or composition is the development in a subject of a humoral and/or a cellular immune response to molecules present in the composition of interest. For purposes of the present invention, a "humoral immune response" refers to an immune response mediated by antibody molecules, while a "cellular immune response" is one mediated by T-lymphocytes and/or other white blood cells. One important aspect of cellular immunity involves an antigen-specific response by cytolytic T-cells ("CTLs"). CTLs have specificity for peptide antigens that are presented in association with proteins encoded by the major histocompatibility complex (MHC) and

expressed on the surfaces of cells. CTLs help induce and promote the intracellular destruction of intracellular microbes, or the lysis of cells infected with such microbes. Another aspect of cellular immunity involves an antigen-specific response by helper T-cells. Helper T-cells act to help stimulate the function, and focus the activity of, nonspecific effector cells against cells displaying peptide antigens in association with MHC molecules on their surface. A “cellular immune response” also refers to the production of cytokines, chemokines and other such molecules produced by activated T-cells and/or other white blood cells, including those derived from CD4+ and CD8+ T-cells.

A composition or vaccine that elicits a cellular immune response may serve to sensitize a vertebrate subject by the presentation of antigen in association with MHC molecules at the cell surface. The cell-mediated immune response is directed at, or near, cells presenting antigen at their surface. In addition, antigen-specific T-lymphocytes can be generated to allow for the future protection of an immunized host.

The ability of a particular antigen to stimulate a cell-mediated immunological response may be determined by a number of assays, such as by lymphoproliferation (lymphocyte activation) assays, CTL cytotoxic cell assays, or by assaying for T-lymphocytes specific for the antigen in a sensitized subject. Such assays are well known in the art. See, e.g., Erickson et al., *J. Immunol.* (1993) 151:4189-4199; Doe et al., *Eur. J. Immunol.* (1994) 24:2369-2376; and the examples below.

Thus, an immunological response as used herein may be one which stimulates the production of CTLs, and/or the production or activation of helper T- cells. The antigen of interest may also elicit an antibody-mediated immune response. Hence, an immunological response may include one or more of the following effects: the production of antibodies by B-cells; and/or the activation of suppressor T-cells and/or $\gamma\delta$ T-cells directed specifically to an antigen or antigens present in the composition or vaccine of interest. These responses may serve to neutralize infectivity, and/or mediate antibody-complement, or antibody dependent cell cytotoxicity (ADCC) to provide protection or alleviation of symptoms to an immunized host. Such responses can be determined using standard immunoassays and neutralization assays, well known in the art.

A "coding sequence" or a sequence which "encodes" a selected polypeptide, is a nucleic acid molecule which is transcribed (in the case of DNA) and translated (in the case of mRNA) into a polypeptide *in vitro* or *in vivo* when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a start codon at the 5' (amino) terminus and a translation stop codon at the 3' (carboxy) terminus. A transcription termination sequence may be located 3' to the coding sequence.

A "nucleic acid" molecule or "polynucleotide" can include both double- and single-stranded sequences and refers to, but is not limited to, cDNA from viral, procaryotic or eucaryotic mRNA, genomic DNA sequences from viral (e.g. DNA viruses and retroviruses) or procaryotic DNA, and especially synthetic DNA sequences. The term also captures sequences that include any of the known base analogs of DNA and RNA.

"Operably linked" refers to an arrangement of elements wherein the components so described are configured so as to perform their desired function. Thus, a given promoter operably linked to a coding sequence is capable of effecting the expression of the coding sequence when the proper transcription factors, etc., are present. The promoter need not be contiguous with the coding sequence, so long as it functions to direct the expression thereof. Thus, for example, intervening untranslated yet transcribed sequences can be present between the promoter sequence and the coding sequence, as can transcribed introns, and the promoter sequence can still be considered "operably linked" to the coding sequence.

"Recombinant" as used herein to describe a nucleic acid molecule means a polynucleotide of genomic, cDNA, viral, semisynthetic, or synthetic origin which, by virtue of its origin or manipulation is not associated with all or a portion of the polynucleotide with which it is associated in nature. The term "recombinant" as used with respect to a protein or polypeptide means a polypeptide produced by expression of a recombinant polynucleotide. In general, the gene of interest is cloned and then expressed in transformed organisms, as described further below. The host organism expresses the foreign gene to produce the protein under expression conditions.

A "control element" refers to a polynucleotide sequence which aids in the expression of a coding sequence to which it is linked. The term includes promoters,

transcription termination sequences, upstream regulatory domains, polyadenylation signals, untranslated regions, including 5'-UTRs and 3'-UTRs and when appropriate, leader sequences and enhancers, which collectively provide for the transcription and translation of a coding sequence in a host cell.

5 A “promoter” as used herein is a DNA regulatory region capable of binding RNA polymerase in a host cell and initiating transcription of a downstream (3' direction) coding sequence operably linked thereto. For purposes of the present invention, a promoter sequence includes the minimum number of bases or elements necessary to initiate transcription of a gene of interest at levels detectable above background. Within the
10 promoter sequence is a transcription initiation site, as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. Eucaryotic promoters will often, but not always, contain “TATA” boxes and “CAT” boxes.

 A control sequence “directs the transcription” of a coding sequence in a cell when RNA polymerase will bind the promoter sequence and transcribe the coding sequence into
15 mRNA, which is then translated into the polypeptide encoded by the coding sequence.

 “Expression cassette” or “expression construct” refers to an assembly which is capable of directing the expression of the sequence(s) or gene(s) of interest. The expression cassette includes control elements, as described above, such as a promoter which is operably linked to (so as to direct transcription of) the sequence(s) or gene(s) of
20 interest, and often includes a polyadenylation sequence as well. Within certain embodiments of the invention, the expression cassette described herein may be contained within a plasmid construct. In addition to the components of the expression cassette, the plasmid construct may also include, one or more selectable markers, a signal which allows the plasmid construct to exist as single-stranded DNA (e.g., a M13 origin of replication), at
25 least one multiple cloning site, and a “mammalian” origin of replication (e.g., a SV40 or adenovirus origin of replication).

 “Transformation,” as used herein, refers to the insertion of an exogenous polynucleotide into a host cell, irrespective of the method used for insertion: for example, transformation by direct uptake, transfection, infection, and the like. For particular
30 methods of transfection, see further below. The exogenous polynucleotide may be

maintained as a nonintegrated vector, for example, an episome, or alternatively, may be integrated into the host genome.

A "host cell" is a cell which has been transformed, or is capable of transformation, by an exogenous DNA sequence.

5 By "isolated" is meant, when referring to a polypeptide, that the indicated molecule is separate and discrete from the whole organism with which the molecule is found in nature or is present in the substantial absence of other biological macromolecules of the same type. The term "isolated" with respect to a polynucleotide is a nucleic acid molecule devoid, in whole or part, of sequences normally associated with it in nature; or a sequence,
10 as it exists in nature, but having heterologous sequences in association therewith; or a molecule disassociated from the chromosome.

The term "purified" as used herein preferably means at least 75% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of biological macromolecules of the same type are
15 present.

"Homology" refers to the percent identity between two polynucleotide or two polypeptide moieties. Two DNA, or two polypeptide sequences are "substantially homologous" to each other when the sequences exhibit at least about 50% , preferably at least about 75%, more preferably at least about 80%-85%, preferably at least about 90%,
20 and most preferably at least about 95%-98%, or more, sequence identity over a defined length of the molecules. As used herein, substantially homologous also refers to sequences showing complete identity to the specified DNA or polypeptide sequence. The term "substantially homologous" as used herein in reference to Δ NS35 generally refers to an HCV nucleic or amino acid sequence that is at least 60% identical to the entire sequence of
25 the polypeptide encoded by Δ NS35 (see FIG. 5), where the sequence identity is preferably at least 75%, more preferably at least 80%, still more preferably at least about 85%, especially more than about 90%, most preferably 95% or greater, particularly 98% or greater. These homologous polypeptides include fragments, including mutants and allelic variants of the fragments. Identity between the two sequences is preferably determined by
30 the Smith-Waterman homology search algorithm as implemented in the MPSRCH program

(Oxford Molecular), using an affine gap search with parameters *gap open penalty*=12 and *gap extension penalty*=1. Thus, for example, the present invention includes an isolate which is 80% identical to a polypeptide encoded by ΔNS35. In some aspects of the invention, the polypeptide of the present invention is substantially homologous to the ΔNS35.

In general, "identity" refers to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Percent identity can be determined by a direct comparison of the sequence information between two molecules by aligning the sequences, counting the exact number of matches between the two aligned sequences, dividing by the length of the shorter sequence, and multiplying the result by 100. Readily available computer programs can be used to aid in the analysis, such as ALIGN, Dayhoff, M.O. in *Atlas of Protein Sequence and Structure* M.O. Dayhoff ed., 5 Suppl. 3:353-358, National biomedical Research Foundation, Washington, DC, which adapts the local homology algorithm of Smith and Waterman *Advances in Appl. Math.* 2:482-489, 1981 for peptide analysis. Programs for determining nucleotide sequence identity are available in the Wisconsin Sequence Analysis Package, Version 8 (available from Genetics Computer Group, Madison, WI) for example, the BESTFIT, FASTA and GAP programs, which also rely on the Smith and Waterman algorithm. These programs are readily utilized with the default parameters recommended by the manufacturer and described in the Wisconsin Sequence Analysis Package referred to above. For example, percent identity of a particular nucleotide sequence to a reference sequence can be determined using the homology algorithm of Smith and Waterman with a default scoring table and a gap penalty of six nucleotide positions.

Another method of establishing percent identity in the context of the present invention is to use the MPSRCH package of programs copyrighted by the University of Edinburgh, developed by John F. Collins and Shane S. Sturrok, and distributed by IntelliGenetics, Inc. (Mountain View, CA). From this suite of packages the Smith-Waterman algorithm can be employed where default parameters are used for the scoring table (for example, gap open penalty of 12, gap extension penalty of one, and a gap of six). From the data generated the "Match" value reflects "sequence identity." Other suitable

programs for calculating the percent identity or similarity between sequences are generally known in the art, for example, another alignment program is BLAST, used with default parameters. For example, BLASTN and BLASTP can be used using the following default parameters: genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; 5 Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + Swiss protein + Spupdate + PIR. Details of these programs can be found at the following internet address: <http://www.ncbi.nlm.gov/cgi-bin/BLAST>.

Alternatively, homology can be determined by hybridization of polynucleotides 10 under conditions which form stable duplexes between homologous regions, followed by digestion with single-stranded-specific nuclease(s), and size determination of the digested fragments. DNA sequences that are substantially homologous can be identified in a Southern hybridization experiment under, for example, stringent conditions, as defined for that particular system. Defining appropriate hybridization conditions is within the skill of 15 the art. See, e.g., Sambrook et al., *supra*; *DNA Cloning, supra*; *Nucleic Acid Hybridization, supra*.

“Stringency” refers to conditions in a hybridization reaction that favor association of very similar sequences over sequences that differ. For example, the combination of temperature and salt concentration should be chosen that is approximately 120 to 200°C 20 below the calculated T_m of the hybrid under study. The temperature and salt conditions can often be determined empirically in preliminary experiments in which samples of genomic DNA immobilized on filters are hybridized to the sequence of interest and then washed under conditions of different stringencies. See Sambrook *et al.* at page 9.50.

Variables to consider when performing, for example, a Southern blot are (1) the 25 complexity of the DNA being blotted and (2) the homology between the probe and the sequences being detected. The total amount of the fragment(s) to be studied can vary a magnitude of 10, from 0.1 to 1 μ g for a plasmid or phage digest to 10^{-9} to 10^{-8} g for a single copy gene in a highly complex eukaryotic genome. For lower complexity polynucleotides, substantially shorter blotting, hybridization, and exposure times, a smaller amount of 30 starting polynucleotides, and lower specific activity of probes can be used. For example, a

single-copy yeast gene can be detected with an exposure time of only 1 hour starting with 1 µg of yeast DNA, blotting for two hours, and hybridizing for 4-8 hours with a probe of 10⁸ cpm/µg. For a single-copy mammalian gene a conservative approach would start with 10 µg of DNA, blot overnight, and hybridize overnight in the presence of 10% dextran sulfate using a probe of greater than 10⁸ cpm/µg, resulting in an exposure time of ~24 hours.

Several factors can affect the melting temperature (T_m) of a DNA-DNA hybrid between the probe and the fragment of interest, and consequently, the appropriate conditions for hybridization and washing. In many cases the probe is not 100% homologous to the fragment. Other commonly encountered variables include the length and total G+C content of the hybridizing sequences and the ionic strength and formamide content of the hybridization buffer. The effects of all of these factors can be approximated by a single equation:

$$T_m = 81 + 16.6(\log_{10} C_i) + 0.4[\%(G + C)] - 0.6(\% \text{formamide}) - 600/n - 1.5(\% \text{mismatch}).$$
where C_i is the salt concentration (monovalent ions) and *n* is the length of the hybrid in base pairs (slightly modified from Meinkoth & Wahl (1984) *Anal. Biochem.* 138: 267-284). In general, convenient hybridization temperatures in the presence of 50% formamide are 42°C for a probe with is 95% to 100% homologous to the target fragment, 37°C for 90% to 95% homology, and 32°C for 85% to 90% homology. For lower homologies, formamide content should be lowered and temperature adjusted accordingly, using the equation above. If the homology between the probe and the target fragment are not known, the simplest approach is to start with both hybridization and wash conditions which are nonstringent. If non-specific bands or high background are observed after autoradiography, the filter can be washed at high stringency and reexposed. If the time required for exposure makes this approach impractical, several hybridization and/or washing stringencies should be tested in parallel.

By "nucleic acid immunization" is meant the introduction of a nucleic acid molecule encoding one or more selected antigens into a host cell, for the *in vivo* expression of the antigen or antigens. The nucleic acid molecule can be introduced directly into the recipient subject, such as by injection, inhalation, oral, intranasal and mucosal administration, or the like, or can be introduced *ex vivo*, into cells which have been

removed from the host. In the latter case, the transformed cells are reintroduced into the subject where an immune response can be mounted against the antigen encoded by the nucleic acid molecule.

An "open reading frame" or ORF is a region of a polynucleotide sequence which encodes a polypeptide; this region can represent a portion of a coding sequence or a total coding sequence.

As used herein, the term "antibody" refers to a polypeptide or group of polypeptides which comprise at least one antigen binding site. An "antigen binding site" is formed from the folding of the variable domains of an antibody molecule(s) to form three-dimensional binding sites with an internal surface shape and charge distribution complementary to the features of an epitope of an antigen, which allows specific binding to form an antibody-antigen complex. An antigen binding site may be formed from a heavy- and/or light-chain domain (VH and VL, respectively), which form hypervariable loops which contribute to antigen binding. The term "antibody" includes, without limitation, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, altered antibodies, univalent antibodies, Fab proteins, and single-domain antibodies. In many cases, the binding phenomena of antibodies to antigens is equivalent to other ligand/anti-ligand binding.

If polyclonal antibodies are desired, a selected mammal (e.g., mouse, rabbit, goat, horse, etc.) is immunized with an immunogenic polypeptide bearing an HCV epitope(s). Serum from the immunized animal is collected and treated according to known procedures. If serum containing polyclonal antibodies to an HCV epitope contains antibodies to other antigens, the polyclonal antibodies can be purified by immunoaffinity chromatography. Techniques for producing and processing polyclonal antisera are known in the art, see for example, Mayer and Walker, eds. (1987) IMMUNOCHEMICAL METHODS IN CELL AND MOLECULAR BIOLOGY (Academic Press, London).

Monoclonal antibodies directed against HCV epitopes can also be readily produced by one skilled in the art. The general methodology for making monoclonal antibodies by hybridomas is well known. Immortal antibody-producing cell lines can be created by cell fusion, and also by other techniques such as direct transformation of B lymphocytes with oncogenic DNA, or transfection with Epstein-Barr virus. See, e.g., M. Schreier et al.

(1980) HYBRIDOMA TECHNIQUES; Hammerling et al. (1981), MONOCLONAL ANTIBODIES AND T-CELL HYBRIDOMAS; Kennett et al. (1980) MONOCLONAL ANTIBODIES; see also, U.S. Pat. Nos. 4,341,761; 4,399,121; 4,427,783; 4,444,887; 4,466,917; 4,472,500; 4,491,632; and 4,493,890. Panels of monoclonal antibodies
5 produced against HCV epitopes can be screened for various properties; i.e., for isotype, epitope affinity, etc. As used herein, a "single domain antibody" (dAb) is an antibody which is comprised of an HL domain, which binds specifically with a designated antigen. A dAb does not contain a VL domain, but may contain other antigen binding domains known to exist to antibodies, for example, the kappa and lambda domains. Methods for
10 preparing dabs are known in the art. See, for example, Ward et al, Nature 341: 544 (1989).

Antibodies can also be comprised of VH and VL domains, as well as other known antigen binding domains. Examples of these types of antibodies and methods for their preparation and known in the art (see, e.g., U.S. Pat. No. 4,816,467, which is incorporated herein by reference), and include the following. For example, "vertebrate antibodies" refers
15 to antibodies which are tetramers or aggregates thereof, comprising light and heavy chains which are usually aggregated in a "Y" configuration and which may or may not have covalent linkages between the chains. In vertebrate antibodies, the amino acid sequences of the chains are homologous with those sequences found in antibodies produced in vertebrates, whether in situ or in vitro (for example, in hybridomas). Vertebrate antibodies
20 include, for example, purified polyclonal antibodies and monoclonal antibodies, methods for the preparation of which are described infra.

"Hybrid antibodies" are antibodies where chains are separately homologous with reference to mammalian antibody chains and represent novel assemblies of them, so that two different antigens are precipitable by the tetramer or aggregate. In hybrid antibodies,
25 one pair of heavy and light chains are homologous to those found in an antibody raised against a first antigen, while a second pair of chains are homologous to those found in an antibody raised against a second antibody. This results in the property of "divalence", i.e., the ability to bind two antigens simultaneously. Such hybrids can also be formed using chimeric chains, as set forth below.

"Chimeric antibodies" refers to antibodies in which the heavy and/or light chains are fusion proteins. Typically, one portion of the amino acid sequences of the chain is homologous to corresponding sequences in an antibody derived from a particular species or a particular class, while the remaining segment of the chain is homologous to the sequences derived from another species and/or class. Usually, the variable region of both light and heavy chains mimics the variable regions or antibodies derived from one species of vertebrates, while the constant portions are homologous to the sequences in the antibodies derived from another species of vertebrates. However, the definition is not limited to this particular example. Also included is any antibody in which either or both of the heavy or light chains are composed of combinations of sequences mimicking the sequences in antibodies of different sources, whether these sources be from differing classes or different species of origin, and whether or not the fusion point is at the variable/constant boundary. Thus, it is possible to produce antibodies in which neither the constant nor the variable region mimic known antibody sequences. It then becomes possible, for example, to construct antibodies whose variable region has a higher specific affinity for a particular antigen, or whose constant region can elicit enhanced complement fixation, or to make other improvements in properties possessed by a particular constant region.

Another example is "altered antibodies", which refers to antibodies in which the naturally occurring amino acid sequence in a vertebrate antibody has been varied. Utilizing recombinant DNA techniques, antibodies can be redesigned to obtain desired characteristics. The possible variations are many, and range from the changing of one or more amino acids to the complete redesign of a region, for example, the constant region. Changes in the constant region, in general, to attain desired cellular process characteristics, e.g., changes in complement fixation, interaction with membranes, and other effector functions. Changes in the variable region can be made to alter antigen binding characteristics. The antibody can also be engineered to aid the specific delivery of a molecule or substance to a specific cell or tissue site. The desired alterations can be made by known techniques in molecular biology, e.g., recombinant techniques, site-directed mutagenesis, etc.

Yet another example are "univalent antibodies", which are aggregates comprised of a heavy-chain/light-chain dimer bound to the Fc (i.e., stem) region of a second heavy chain. This type of antibody escapes antigenic modulation. See, e.g., Glennie et al. Nature 295: 712 (1982). Included also within the definition of antibodies are "Fab" fragments of antibodies. The "Fab" region refers to those portions of the heavy and light chains which are roughly equivalent, or analogous, to the sequences which comprise the branch portion of the heavy and light chains, and which have been shown to exhibit immunological binding to a specified antigen, but which lack the effector Fc portion. "Fab" includes aggregates of one heavy and one light chain (commonly known as Fab'), as well as tetramers containing the 2H and 2L chains (referred to as F(ab)2), which are capable of selectively reacting with a designated antigen or antigen family. Fab antibodies can be divided into subsets analogous to those described above, i.e., "vertebrate Fab", "hybrid Fab", "chimeric Fab", and "altered Fab". Methods of producing Fab fragments of antibodies are known within the art and include, for example, proteolysis, and synthesis by recombinant techniques.

"Antigen-antibody complex" refers to the complex formed by an antibody that is specifically bound to an epitope on an antigen.

"Immunogenic polypeptide" refers to a polypeptide that elicits a cellular and/or humoral immune response in a mammal, whether alone or linked to a carrier, in the presence or absence of an adjuvant.

"Antigenic determinant" refers to the site on an antigen or hapten to which a specific antibody molecule or specific cell surface receptor binds.

As used herein, "treatment" refers to any of (i) the prevention of infection or reinfection, as in a traditional vaccine, (ii) the reduction or elimination of symptoms, and (iii) the substantial or complete elimination of the pathogen in question. Treatment may be effected prophylactically (prior to infection) or therapeutically (following infection).

By "vertebrate subject" is meant any member of the subphylum cordata, including, without limitation, humans and other primates, including non-human primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including

rodents such as mice, rats and guinea pigs; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like. The term does not denote a particular age. Thus, both adult and newborn individuals are intended to be covered. The invention described herein is intended for use in any of the
5 above vertebrate species, since the immune systems of all of these vertebrates operate similarly.

II. Modes of Carrying out the Invention

Before describing the present invention in detail, it is to be understood that this
10 invention is not limited to particular formulations or process parameters as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

Although a number of compositions and methods similar or equivalent to those
15 described herein can be used in the practice of the present invention, the preferred materials and methods are described herein.

General Overview

An aim of an HCV vaccine is to generate broad immunity to a wide breadth of
20 antigens because HCV is so divergent and because humoral as well as cellular immune responses are desirable to combat this human pathogen. While antibodies generated against the envelope glycoprotein(s) might aid in virus neutralization, there is additional benefit to be derived from a vaccine that includes other regions. The likelihood of T-helper responses generated against a polypeptide would be helpful in a vaccine setting as would
25 generation of cytotoxic T cells. The non-structural region represents such a candidate antigen, but processing by the protease generates several polypeptides, making purification complicated. It would be advantageous, therefore, to derive a non-structural cassette that is unprocessed by the NS3 protease.

The present invention solves this and other problems using compositions and
30 methods involving an N-terminal deletion in NS3, which removes the catalytic domain.

As such, some or all of the remainder of the non-structural region (through NS5B) is expressed as an intact polypeptide. Expression of this species has been documented in mammalian cells as well as in yeast. Further, in certain aspects, polynucleotides encoding HCV core polypeptides (or fragments thereof) are added (*e.g.*, operably linked) to the carboxy-terminus of the non-structural cassette. As the core coding region is relatively highly conserved among HCV isolates, the presence of this region may enhance the immune response. Because core has at its C-terminus a very hydrophobic domain (amino acids 174-191), shorter versions of core were also engineered onto the polypeptide. As described in detail herein, the truncation of core to amino acid 121 yielded higher expression than the amino acid 173 truncation when engineered onto the C-terminus of the mutant NS polypeptide. The combination of most of the non-structural region fused to a C-terminally truncated core into a polypeptide is novel and has advantages for vaccine immunization. Moreover, because the aim is not necessarily to generate antibody responses to this polypeptide, there is no need to maintain a native conformation, enabling a more facile purification protocol.

Mutant HCV Non-Structural Polypeptides

Genomes of HCV strains contain a single open reading frame of approximately 9,000 to 12,000 nucleotides, which is transcribed into a polyprotein. An HCV polyprotein is cleaved to produce at least ten distinct products, in the order of NH₂- Core-E1-E2-p7-NS2-NS3-NS4a-NS4b-NS5a-NS5b-COOH. Mutant HCV polypeptides of the invention contain an N-terminal deletion in NS3, which removes or disables the catalytic domain. Preferably, the polypeptides also include the remainder of the non-structural region, although in certain embodiments, the polypeptides may include less than all of the remaining NS polypeptides, for example mutant NS polypeptides including any combinations of NS2-NS3-NS4a-NS4b-NS5a-NS5b (*e.g.*, NS3NS3-NS5a-NS5b; NS3-NS4a-NS4b; NS3-NS4a-NS4b-NS5a; NS3-NS4b-NS5a-NS5b; NS3-NS4a-NS5a; NS3-NS4b-NS5a; NS3-NS4b-NS5b; etc.).

The HCV NS3 protein functions as a protease and a helicase and occurs at approximately amino acid 1027 to amino acid 1657 of the polyprotein (numbered relative

to HCV-1). See Choo *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:2451-2455. HCV NS4 occurs at approximately amino acid 1658 to amino acid 1972, NS5a occurs at approximately amino acid 1973 to amino acid 2420, and HCV NS5b occurs at approximately amino acid 2421 to amino acid 3011 of the polyprotein (numbered relative to HCV-1) (Choo *et al.*, 1991).

The mutant polypeptides described herein can either be full-length polypeptides or portions of NS3, NS4 (NS4a and NS4b), NS5a, and NS5b polypeptides. Epitopes of NS3, NS4 (NS4a and NS4b), NS5a, NS5b, NS3NS4NS5a, and NS3NS4NS5aNS5b can be identified by several methods. For example, NS3, NS4, NS5a, NS5b polypeptides or fusion proteins comprising any combination of the above, can be isolated, for example, by immunoaffinity purification using a monoclonal antibody for the polypeptide or protein. The isolated protein sequence can then be screened by preparing a series of short peptides by proteolytic cleavage of the purified protein, which together span the entire protein sequence. By starting with, for example, 100-mer polypeptides, each polypeptide can be tested for the presence of epitopes recognized by a T cell receptor on an HCV-activated T cell, progressively smaller and overlapping fragments can then be tested from an identified 100-mer to map the epitope of interest.

Epitopes recognized by a T cell receptor on an HCV-activated T cell can be identified by, for example, ⁵¹Cr release assay (see Example 2) or by lymphoproliferation assay (see Example 4). In a ⁵¹Cr release assay, target cells can be constructed that display the epitope of interest by cloning a polynucleotide encoding the epitope into an expression vector and transforming the expression vector into the target cells. Non-structural polypeptides can occur in any order in the fusion protein. If desired, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more of one or more of the polypeptides may occur in the fusion protein. Multiple viral strains of HCV occur, and NS3, NS4, NS5a, and NS5b polypeptides of any of these strains can be used in a fusion protein.

Nucleic acid and amino acid sequences of a number of HCV strains and isolates, including nucleic acid and amino acid sequences of NS3, NS4, NS5a, NS5b genes and polypeptides have been determined. For example, isolate HCV J1.1 is described in Kubo *et al.* (1989) Japan. Nucl. Acids Res. 17:10367-10372; Takeuchi *et al.* (1990) Gene

91:287-291; Takeuchi *et al.* (1990) J. Gen. Virol. 71:3027-3033; and Takeuchi *et al.* (1990) Nucl. Acids Res. 18:4626. The complete coding sequences of two independent isolates, HCV-J and BK, are described by Kato *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:9524-9528 and Takamizawa *et al.*, (1991) J. Virol. 65:1105-1113 respectively.

5 Publications that describe HCV-1 isolates include Choo *et al.* (1990) Brit. Med. Bull. 46:423-441; Choo *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:2451-2455 and Han *et al.* (1991) Proc. Natl. Acad. Sci. USA 88:1711-1715. HCV isolates HC-J1 and HC-J4 are described in Okamoto *et al.* (1991) Japan J. Exp. Med. 60:167-177. HCV isolates HCT 18~, HCT 23, Th, HCT 27, EC1 and EC10 are described in Weiner *et al.* (1991) Virol. 10 180:842-848. HCV isolates Pt-1, HCV-K1 and HCV-K2 are described in Enomoto *et al.* (1990) Biochem. Biophys. Res. Commun. 170:1021-1025. HCV isolates A, C, D & E are described in Tsukiyama-Kohara *et al.* (1991) Virus Genes 5:243-254.

Each of the mutant HCV polypeptides containing at least portions of NS3, NS4 and NS5 can be obtained from the same HCV strain or isolate or from different HCV strains or isolates. Thus, each non-structural region of the polypeptide can be from the same HCV 15 strain or isolate or from each different HCV strains or isolates. In addition to the mutant HCV non-structural polypeptides described herein, the proteins can contain other polypeptides derived from the HCV polyprotein. For example, it may be desirable to include polypeptides derived from the core region of the HCV polyprotein. This region 20 occurs at amino acid positions 1-191 of the HCV polyprotein, numbered relative to HCV-1. Either the full-length protein or epitopes of the full-length protein may be used in the subject fusions, such as those epitopes found between amino acids 10-53, amino acids 10-45, amino acids 67-88, amino acids 120-130, or any of the core epitopes identified in, e.g., Houghton *et al.*, U.S. Patent No. 5,350,671; Chien *et al.*, *Proc. Natl. Acad. Sci. USA* (1992) 25 89:10011-10015; Chien *et al.*, *J. Gastroent. Hepatol.* (1993) 8:S33-39; Chien *et al.*, International Publication No. WO 93/00365; Chien, D.Y., International Publication No. WO 94/01778; and commonly owned, U.S. Patent No. 6,150,087, the disclosures of which are incorporated herein by reference in their entireties. When present, additional non-structural HCV polypeptides such as core can be obtained from the same HCV strain or 30 isolate or from different HCV strains or isolates.

Preferably, the above-described mutant proteins, as well as the individual components of these proteins, are produced recombinantly. A polynucleotide encoding these proteins can be introduced into an expression vector which can be expressed in a suitable expression system. A variety of bacterial, yeast, mammalian, insect and plant expression systems are available in the art and any such expression system can be used. Optionally, a polynucleotide encoding these proteins can be translated in a cell-free translation system. Such methods are well known in the art. The proteins also can be constructed by solid phase protein synthesis.

If desired, the mutant polypeptides, or the individual components of these polypeptides, also can contain other amino acid sequences, such as amino acid linkers or signal sequences, as well as ligands useful in protein purification, such as glutathione-S-transferase and staphylococcal protein A.

Polynucleotides

The polynucleotides of the present invention are not necessarily physically derived from the nucleotide sequences shown, but can be generated in any manner, including, for example, chemical synthesis or DNA replication or reverse transcription or transcription. In addition, combinations of regions corresponding to that of the designated sequences can be modified in ways known to the art to be consistent with an intended use.

The DNA encoding the desired polypeptide, whether in fused or mature form, and whether or not containing a signal sequence to permit secretion, can be ligated into expression vectors suitable for any convenient host. Both eukaryotic and prokaryotic host systems are presently used in forming recombinant polypeptides, and a summary of some of the more common control systems and host cell is given below. The polypeptide produced in such host cells is then isolated from lysed cells or from the culture medium and purified to the extent needed for its intended use.

Purification can be by techniques known in the art, for example, differential extraction, salt fractionation, chromatography on ion exchange resins, affinity chromatography, centrifugation, alkali resolubilization of insoluble protein, and the like.

See, for example, Methods in Enzymology for a variety of methods for purifying proteins.

Polynucleotides contain less than an entire HCV genome and can be RNA or single- or double-stranded DNA. Preferably, the polynucleotides are isolated free of other components, such as proteins and lipids. Polynucleotides of the invention can also comprise other nucleotide sequences, such as sequences coding for linkers, signal
5 sequences, or ligands useful in protein purification such as glutathione-S-transferase and staphylococcal protein A.

Polynucleotides encoding mutant HCV non-structural polypeptides can be isolated from a genomic library derived from nucleic acid sequences present in, for example, the plasma, serum, or liver homogenate of an HCV infected individual or can be synthesized in
10 the laboratory, for example, using an automatic synthesizer. An amplification method such as PCR can be used to amplify polynucleotides from either HCV genomic DNA or cDNA.

Further, while the polypeptides that are not NS3, NS4, or NS5 of HCV of the present invention can comprise a substantially complete viral domain, in many applications all that is required is that the polypeptide comprise an antigenic or immunogenic region of
15 the virus. An antigenic region of a polypeptide is generally relatively small-typically 8 to 10 amino acids or less in length. Fragments of as few as 5 amino acids can characterize an antigenic region. These segments can correspond to regions of, for example, C, E1, or E2 epitopes. Accordingly, using the cDNAs of C, E1, or E2 as a basis, DNAs encoding short segments of C, E1, or E2 polypeptides can be expressed recombinantly either as fusion
20 proteins, or as isolated polypeptides. In addition, short amino acid sequences can be conveniently obtained by chemical synthesis.

Polynucleotides encoding the polypeptides described herein can comprise coding sequences for these polypeptides which occur naturally or can be artificial sequences which do not occur in nature. These polynucleotides can be ligated to form a coding sequence for
25 the fusion proteins using standard molecular biology techniques. If desired, polynucleotides can be cloned into an expression vector and transformed into, for example, bacterial, yeast, insect, plant or mammalian cells so that the fusion proteins of the invention can be expressed in and isolated from a cell culture.

The expression of polypeptides containing these domains in a variety of
30 recombinant host cells, including, for example, bacteria, yeast, insect, plant and vertebrate

cells, give rise to important immunological reagents which can be used for diagnosis, detection, and vaccines.

The general techniques used in extracting the genome from a virus, preparing and probing a cDNA library, sequencing clones, constructing expression vectors, transforming
5 cells, performing immunological assays such as radioimmunoassays and. ELISA assays, for growing cells in culture, and the like are known in the art and laboratory manuals are available describing these techniques. However, as a general guide, the following sets forth some sources currently available for such procedures, and for materials useful in carrying them out.

10 Both prokaryotic and eukaryotic host cells may be used for expression of desired coding sequences when appropriate control sequences which are compatible with the designated host are used. Among prokaryotic hosts, *E. coli* is most frequently used. Expression control sequences for prokaryotes include promoters, optionally containing operator portions, and ribosome binding sites. Transfer vectors compatible with
15 prokaryotic hosts are commonly derived from, for example, pBR322, a plasmid containing operons conferring ampicillin and tetracycline resistance, and the various pUC vectors, which also contain sequences conferring antibiotic resistance markers. These markers may be used to obtain successful transformants by selection. Commonly used prokaryotic control sequences include the Beta-lactamase (penicillinase) and lactose promoter systems
20 (Chang et al. (1977), *Nature* 198:1056), the tryptophan (*trp*) promoter system (Goeddel et al. (1980) *Nucleic Acid Res.* 8:4057), the lambda-derived P[L] promoter and N gene ribosome binding site (Shimatake et al. (1981) *Nature* 292:128) and the hybrid *tac* promoter (De Boer et al. (1983) *Proc. Natl. Acad. Sci. U.S.A.* 292:128) derived from sequences of the *trp* and *lac* UV5 promoters. The foregoing systems are particularly
25 compatible with *E. coli*; if desired, other prokaryotic hosts such as strains of *Bacillus* or *Pseudomonas* may be used, with corresponding control sequences.

Eukaryotic hosts include mammalian and yeast cells in culture systems. Mammalian cell lines available as hosts for expression are known in the art and include many immortalized cell lines available from the American Type Culture Collection
30 (ATCC), including HeLa cells, Chinese hamster ovary (CHO) cells, baby hamster kidney

(BHK) cells, and a number of other cell lines. Suitable promoters for mammalian cells are also known in the art and include viral promoters such as that from Simian Virus 40 (SV40) (Fiers (1978), Nature 273:113), Rous sarcoma virus (RSV), adenovirus (ADV), and bovine papilloma virus (BPV). Mammalian cells may also require terminator
5 sequences and poly A addition sequences; enhancer sequences which increase expression may also be included, and sequences which cause amplification of the gene may also be desirable. These sequences are known in the art. Vectors suitable for replication in mammalian cells may include viral replicons, or sequences which insure integration of the appropriate sequences encoding NANBV epitopes into the host genome.

10 The vaccinia virus system can also be used to express foreign DNA in mammalian cells. To express heterologous genes, the foreign DNA is usually inserted into the thymidine kinase gene of the vaccinia virus and then infected cells can be selected. This procedure is known in the art and further information can be found in these references (Mackett et al. J. Virol. 49: 857-864 (1984) and Chapter 7 in DNA Cloning, Vol. 2, IRL
15 Press).

Yeast expression systems are also known to one of ordinary skill in the art. A yeast promoter is any DNA sequence capable of binding yeast RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*e.g.*, structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to
20 the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site (the "TATA Box") and a transcription initiation site. A yeast promoter may also have a second domain called an upstream activator sequence (UAS), which, if present, is usually distal to the structural gene. The UAS permits regulated (inducible) expression. Constitutive expression occurs in the absence of a UAS.
25 Regulated expression may be either positive or negative, thereby either enhancing or reducing transcription.

Yeast is a fermenting organism with an active metabolic pathway, therefore sequences encoding enzymes in the metabolic pathway provide particularly useful promoter sequences. Examples include alcohol dehydrogenase (ADH) (EP-A-0 284 044),
30 enolase, glucokinase, glucose-6-phosphate isomerase, glyceraldehyde-3-phosphate-

dehydrogenase (GAP or GAPDH), hexokinase, phosphofructokinase, 3-phosphoglycerate mutase, and pyruvate kinase (PyK) (EPO-A-0 329 203). The yeast *PHO5* gene, encoding acid phosphatase, also provides useful promoter sequences (Myanohara *et al.* (1983) *Proc. Natl. Acad. Sci. USA* 80:1).

5 In addition, synthetic promoters which do not occur in nature also function as yeast promoters. For example, UAS sequences of one yeast promoter may be joined with the transcription activation region of another yeast promoter, creating a synthetic hybrid promoter. Examples of such hybrid promoters include the ADH regulatory sequence linked to the GAP transcription activation region (US Patent Nos. 4,876,197 and
10 4,880,734). Other examples of hybrid promoters include promoters which consist of the regulatory sequences of either the *ADH2*, *GAL4*, *GAL10*, OR *PHO5* genes, combined with the transcriptional activation region of a glycolytic enzyme gene such as GAP or PyK (EP-A-0 164 556). Furthermore, a yeast promoter can include naturally occurring promoters of non-yeast origin that have the ability to bind yeast RNA polymerase and initiate
15 transcription. Examples of such promoters include, *inter alia*, (Cohen *et al.* (1980) *Proc. Natl. Acad. Sci. USA* 77:1078; Henikoff *et al.* (1981) *Nature* 283:835; Hollenberg *et al.* (1981) *Curr. Topics Microbiol. Immunol.* 96:119; Hollenberg *et al.* (1979) "The Expression of Bacterial Antibiotic Resistance Genes in the Yeast *Saccharomyces cerevisiae*," in: *Plasmids of Medical, Environmental and Commercial Importance* (eds.
20 K.N. Timmis and A. Puhler); Mercerau-Puigalon *et al.* (1980) *Gene* 11:163; Panthier *et al.* (1980) *Curr. Genet.* 2:109).

 A DNA molecule may be expressed intracellularly in yeast. A promoter sequence may be directly linked with the DNA molecule, in which case the first amino acid at the N-terminus of the recombinant protein will always be a methionine, which is encoded by the
25 ATG start codon. If desired, methionine at the N-terminus may be cleaved from the protein by *in vitro* incubation with cyanogen bromide.

 Fusion proteins provide an alternative for yeast expression systems, as well as in mammalian, baculovirus, and bacterial expression systems. Usually, a DNA sequence encoding the N-terminal portion of an endogenous yeast protein, or other stable protein, is
30 fused to the 5' end of heterologous coding sequences. Upon expression, this construct will

provide a fusion of the two amino acid sequences. For example, the yeast or human superoxide dismutase (SOD) gene, can be linked at the 5' terminus of a foreign gene and expressed in yeast. The DNA sequence at the junction of the two amino acid sequences may or may not encode a cleavable site. See *e.g.*, EP-A-0 196 056. Another example is a ubiquitin fusion protein. Such a fusion protein is made with the ubiquitin region that preferably retains a site for a processing enzyme (*e.g.*, ubiquitin-specific processing protease) to cleave the ubiquitin from the foreign protein. Through this method, therefore, native foreign protein can be isolated (*e.g.*, WO88/024066).

Alternatively, foreign proteins can also be secreted from the cell into the growth media by creating chimeric DNA molecules that encode a fusion protein comprised of a leader sequence fragment that provide for secretion in yeast of the foreign protein. Preferably, there are processing sites encoded between the leader fragment and the foreign gene that can be cleaved either *in vivo* or *in vitro*. The leader sequence fragment usually encodes a signal peptide comprised of hydrophobic amino acids which direct the secretion of the protein from the cell.

DNA encoding suitable signal sequences can be derived from genes for secreted yeast proteins, such as the yeast invertase gene (EP-A-0 012 873; JPO. 62,096,086) and the A-factor gene (US patent 4,588,684). Alternatively, leaders of non-yeast origin, such as an interferon leader, exist that also provide for secretion in yeast (EP-A-0 060 057).

A preferred class of secretion leaders are those that employ a fragment of the yeast alpha-factor gene, which contains both a "pre" signal sequence, and a "pro" region. The types of alpha-factor fragments that can be employed include the full-length pre-pro alpha factor leader (about 83 amino acid residues) as well as truncated alpha-factor leaders (usually about 25 to about 50 amino acid residues) (US Patents 4,546,083 and 4,870,008; EP-A-0 324 274). Additional leaders employing an alpha-factor leader fragment that provides for secretion include hybrid alpha-factor leaders made with a presequence of a first yeast, but a pro-region from a second yeast alphafactor. (*e.g.*, see WO 89/02463.)

Usually, transcription termination sequences recognized by yeast are regulatory regions located 3' to the translation stop codon, and thus together with the promoter flank the coding sequence. These sequences direct the transcription of an mRNA which can be

translated into the polypeptide encoded by the DNA. Examples of transcription terminator sequence and other yeast-recognized termination sequences, such as those coding for glycolytic enzymes.

Usually, the above described components, comprising a promoter, leader (if desired), coding sequence of interest, and transcription termination sequence, are put together into expression constructs. Expression constructs are often maintained in a replicon, such as an extrachromosomal element (*e.g.*, plasmids) capable of stable maintenance in a host, such as yeast or bacteria. The replicon may have two replication systems, thus allowing it to be maintained, for example, in yeast for expression and in a prokaryotic host for cloning and amplification. Examples of such yeast-bacteria shuttle vectors include YEp24 (Botstein *et al.* (1979) *Gene* 8:17-24), pCl/1 (Brake *et al.* (1984) *Proc. Natl. Acad. Sci USA* 81:4642-4646), and YRp17 (Stinchcomb *et al.* (1982) *J. Mol. Biol.* 158:157). In addition, a replicon may be either a high or low copy number plasmid. A high copy number plasmid will generally have a copy number ranging from about 5 to about 200, and usually about 10 to about 150. A host containing a high copy number plasmid will preferably have at least about 10, and more preferably at least about 20. Enter a high or low copy number vector may be selected, depending upon the effect of the vector and the foreign protein on the host. See *e.g.*, Brake *et al.*, *supra*.

Alternatively, the expression constructs can be integrated into the yeast genome with an integrating vector. Integrating vectors usually contain at least one sequence homologous to a yeast chromosome that allows the vector to integrate, and preferably contain two homologous sequences flanking the expression construct. Integrations appear to result from recombinations between homologous DNA in the vector and the yeast chromosome (Orr-Weaver *et al.* (1983) *Methods in Enzymol.* 101:228-245). An integrating vector may be directed to a specific locus in yeast by selecting the appropriate homologous sequence for inclusion in the vector. See Orr-Weaver *et al.*, *supra*. One or more expression construct may integrate, possibly affecting levels of recombinant protein produced (Rine *et al.* (1983) *Proc. Natl. Acad. Sci. USA* 80:6750). The chromosomal sequences included in the vector can occur either as a single segment in the vector, which results in the integration of the entire vector, or two segments homologous to adjacent

segments in the chromosome and flanking the expression construct in the vector, which can result in the stable integration of only the expression construct.

Usually, extrachromosomal and integrating expression constructs may contain selectable markers to allow for the selection of yeast strains that have been transformed.

5 Selectable markers may include biosynthetic genes that can be expressed in the yeast host, such as *ADE2*, *HIS4*, *LEU2*, *TRP1*, and *ALG7*, and the G418 resistance gene, which confer resistance in yeast cells to tunicamycin and G418, respectively. In addition, a suitable selectable marker may also provide yeast with the ability to grow in the presence of toxic compounds, such as metal. For example, the presence of *CUP1* allows yeast to grow in the
10 presence of copper ions (Butt *et al.* (1987) *Microbiol. Rev.* 51:351).

Alternatively, some of the above described components can be put together into transformation vectors. Transformation vectors are usually comprised of a selectable marker that is either maintained in a replicon or developed into an integrating vector, as described above.

15 Expression and transformation vectors, either extrachromosomal replicons or integrating vectors, have been developed for transformation into many yeasts. For example, expression vectors have been developed for, *inter alia*, the following yeasts: *Candida albicans* (Kurtz, *et al.* (1986) *Mol. Cell. Biol.* 6:142), *Candida maltosa* (Kunze, *et al.* (1985) *J. Basic Microbiol.* 25:141). *Hansenula polymorpha* (Gleeson, *et al.* (1986) *J. Gen. Microbiol.* 132:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet.* 202:302),
20 *Kluyveromyces fragilis* (Das, *et al.* (1984) *J. Bacteriol.* 158:1165), *Kluyveromyces lactis* (De Louvencourt *et al.* (1983) *J. Bacteriol.* 154:737; Van den Berg *et al.* (1990) *Bio/Technology* 8:135), *Pichia guillermondii* (Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141), *Pichia pastoris* (Cregg, *et al.* (1985) *Mol. Cell. Biol.* 5:3376; US Patent Nos.
25 4,837,148 and 4,929,555), *Saccharomyces cerevisiae* (Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA* 75:1929; Ito *et al.* (1983) *J. Bacteriol.* 153:163), *Schizosaccharomyces pombe* (Beach and Nurse (1981) *Nature* 300:706), and *Yarrowia lipolytica* (Davidow, *et al.* (1985) *Curr. Genet.* 10:380471 Gaillardin, *et al.* (1985) *Curr. Genet.* 10:49).

Methods of introducing exogenous DNA into yeast hosts are well-known in the art,
30 and usually include either the transformation of spheroplasts or of intact yeast cells treated

with alkali cations. Transformation procedures usually vary with the yeast species to be transformed. (See *e.g.*, Kurtz *et al.* (1986) *Mol. Cell. Biol.* 6:142; Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141; Candida; Gleeson *et al.* (1986) *J. Gen. Microbiol.* 132:3459; Roggenkamp *et al.* (1986) *Mol. Gen. Genet.* 202:302; Hansenula; Das *et al.* (1984) *J. Bacteriol.* 158:1165; De Louvencourt *et al.* (1983) *J. Bacteriol.* 154:1165; Van den Berg *et al.* (1990) *Bio/Technology* 8:135; Kluyveromyces; Cregg *et al.* (1985) *Mol. Cell. Biol.* 5:3376; Kunze *et al.* (1985) *J. Basic Microbiol.* 25:141; US Patent Nos. 4,837,148 and 4,929,555; Pichia; Hinnen *et al.* (1978) *Proc. Natl. Acad. Sci. USA* 75:1929; Ito *et al.* (1983) *J. Bacteriol.* 153:163 Saccharomyces; Beach and Nurse (1981) *Nature* 300:706; Schizosaccharomyces; Davidow *et al.* (1985) *Curr. Genet.* 10:39; Gaillardin *et al.* (1985) *Curr. Genet.* 10:49; Yarrowia).

Bacterial expression techniques are known in the art. A bacterial promoter is any DNA sequence capable of binding bacterial RNA polymerase and initiating the downstream (3') transcription of a coding sequence (*e.g.*, structural gene) into mRNA. A promoter will have a transcription initiation region which is usually placed proximal to the 5' end of the coding sequence. This transcription initiation region usually includes an RNA polymerase binding site and a transcription initiation site. A bacterial promoter may also have a second domain called an operator, that may overlap an adjacent RNA polymerase binding site at which RNA synthesis begins. The operator permits negative regulated (inducible) transcription, as a gene repressor protein may bind the operator and thereby inhibit transcription of a specific gene. Constitutive expression may occur in the absence of negative regulatory elements, such as the operator. In addition, positive regulation may be achieved by a gene activator protein binding sequence, which, if present is usually proximal (5') to the RNA polymerase binding sequence. An example of a gene activator protein is the catabolite activator protein (CAP), which helps initiate transcription of the lac operon in *Escherichia coli* (*E. coli*) (Raibaud *et al.* (1984) *Annu. Rev. Genet.* 18:173). Regulated expression may therefore be either positive or negative, thereby either enhancing or reducing transcription.

Expression and transformation vectors, either extra-chromosomal replicons or integrating vectors, have been developed for transformation into many bacteria. For

example, expression vectors have been developed for, *inter alia*, the following bacteria:

Bacillus subtilis (Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA* 79:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541), Escherichia coli (Shimatake *et al.* (1981) *Nature* 292:128; Amann *et al.* (1985) *Gene* 40:183; Studier *et al.* (1986) *J. Mol. Biol.* 189:113; EP-A-0 036 776, EP-A-0 136 829 and EP-A-0 136 907), Streptococcus cremoris (Powell *et al.* (1988) *Appl. Environ. Microbiol.* 54:655); Streptococcus lividans (Powell *et al.* (1988) *Appl. Environ. Microbiol.* 54:655), Streptomyces lividans (US patent 4,745,056).

Methods of introducing exogenous DNA into bacterial hosts are well-known in the art, and usually include either the transformation of bacteria treated with CaCl₂ or other agents, such as divalent cations and DMSO. DNA can also be introduced into bacterial cells by electroporation. Transformation procedures usually vary with the bacterial species to be transformed. (See *e.g.*, Masson *et al.* (1989) *FEMS Microbiol. Lett.* 60:273; Palva *et al.* (1982) *Proc. Natl. Acad. Sci. USA* 79:5582; EP-A-0 036 259 and EP-A-0 063 953; WO 84/04541, Bacillus, Miller *et al.* (1988) *Proc. Natl. Acad. Sci.* 85:856; Wang *et al.* (1990) *J. Bacteriol.* 172:949; Campylobacter, Cohen *et al.* (1973) *Proc. Natl. Acad. Sci.* 69:2110; Dower *et al.* (1988) *Nucleic Acids Res.* 16:6127; Kushner (1978) "An improved method for transformation of Escherichia coli with ColE1-derived plasmids. In *Genetic Engineering: Proceedings of the International Symposium on Genetic Engineering* (eds. H.W. Boyer and S. Nicosia); Mandel *et al.* (1970) *J. Mol. Biol.* 53:159; Taketo (1988) *Biochim. Biophys. Acta* 949:318; Escherichia; Chassy *et al.* (1987) *FEMS Microbiol. Lett.* 44:173 Lactobacillus; Fiedler *et al.* (1988) *Anal. Biochem* 170:38, Pseudomonas; Augustin *et al.* (1990) *FEMS Microbiol. Lett.* 66:203, Staphylococcus, Barany *et al.* (1980) *J. Bacteriol.* 144:698; Harlander (1987) "Transformation of Streptococcus lactis by electroporation, in: *Streptococcal Genetics* (ed. J. Ferretti and R. Curtiss III); Perry *et al.* (1981) *Infect. Immun.* 32:1295; Powell *et al.* (1988) *Appl. Environ. Microbiol.* 54:655; Somkuti *et al.* (1987) *Proc. 4th Evr. Cong. Biotechnology* 1:412, Streptococcus).

In addition, viral antigens can be expressed in insect cells by the Baculovirus system. A general guide to Baculovirus expression by Summer and Smith is A Manual of

Methods for Baculovirus Vectors and Insect Cell Culture Procedures (Texas Agricultural Experiment Station Bulletin No. 1555). To incorporate the heterologous gene into the Baculovirus genome the gene is first cloned into a transfer vector containing some Baculovirus sequences. This transfer vector, when it is cotransfected with wild-type virus
5 into insect cells, will recombine with the wild-type virus. Usually, the transfer vector will be engineered so that the heterologous gene will disrupt the wild-type Baculovirus polyhedron gene. This disruption enables easy selection of the recombinant virus since the cells infected with the recombinant virus will appear phenotypically different from the cells infected with the wild-type virus. The purified recombinant virus can be used to infect cells
10 to express the heterologous gene. The foreign protein can be secreted into the medium if a signal peptide is linked in frame to the heterologous gene; otherwise, the protein will be bound in the cell lysates. For further information, see Smith et al Mol. & Cell. Biol. 3:2156-2165 (1983) or Luckow and Summers in Virology 17: 31-39 (1989).

Baculovirus expression can also be affected in plant cells. There are many plant
15 cell culture and whole plant genetic expression systems known in the art. Exemplary plant cellular genetic expression systems include those described in patents, such as: US 5,693,506; US 5,659,122; and US 5,608,143. Additional examples of genetic expression in plant cell culture has been described by Zenk, *Phytochemistry* 30:3861-3863 (1991). Descriptions of plant protein signal peptides may be found in addition to the references
20 described above in Vaulcombe et al., *Mol. Gen. Genet.* 209:33-40 (1987); Chandler et al., *Plant Molecular Biology* 3:407-418 (1984); Rogers, *J. Biol. Chem.* 260:3731-3738 (1985); Rothstein et al., *Gene* 55:353-356 (1987); Whittier et al., *Nucleic Acids Research* 15:2515-2535 (1987); Wirsal et al., *Molecular Microbiology* 3:3-14 (1989); Yu et al., *Gene* 122:247-253 (1992). A description of the regulation of plant gene expression by the
25 phytohormone, gibberellic acid and secreted enzymes induced by gibberellic acid can be found in R.L. Jones and J. MacMillin, Gibberellins: in: *Advanced Plant Physiology*, Malcolm B. Wilkins, ed., 1984 Pitman Publishing Limited, London, pp. 21-52. References that describe other metabolically-regulated genes: Sheen, *Plant Cell*, 2:1027-1038(1990); Maas et al., *EMBO J.* 9:3447-3452 (1990); Benkel and Hickey, *Proc. Natl.*
30 *Acad. Sci.* 84:1337-1339 (1987).

All plants from which protoplasts can be isolated and cultured to give whole regenerated plants can be transformed by the present invention so that whole plants are recovered which contain the transferred gene. It is known that practically all plants can be regenerated from cultured cells or tissues, including but not limited to all major species of
5 sugarcane, sugar beet, cotton, fruit and other trees, legumes and vegetables. Some suitable plants include, for example, species from the genera *Fragaria*, *Lotus*, *Medicago*, *Onobrychis*, *Trifolium*, *Trigonella*, *Vigna*, *Citrus*, *Linum*, *Geranium*, *Manihot*, *Daucus*, *Arabidopsis*, *Brassica*, *Raphanus*, *Sinapis*, *Atropa*, *Capsicum*, *Datura*, *Hyoscyamus*, *Lycopersion*, *Nicotiana*, *Solanum*, *Petunia*, *Digitalis*, *Majorana*, *Cichorium*, *Helianthus*,
10 *Lactuca*, *Bromus*, *Asparagus*, *Antirrhinum*, *Hererocallis*, *Nemesia*, *Pelargonium*, *Panicum*, *Pennisetum*, *Ranunculus*, *Senecio*, *Salpiglossis*, *Cucumis*, *Browaalia*, *Glycine*, *Lolium*, *Zea*, *Triticum*, *Sorghum*, and *Datura*.

Transformation can be by any method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus and transducing a host
15 cell with the virus, and by direct uptake of the polynucleotide. The transformation procedure used depends upon the host to be transformed. Bacterial transformation by direct uptake generally employs treatment with calcium or rubidium chloride (Cohen (1972), Proc. Natl. Acad. Sci. U.S.A. 69:2110; Maniatis et al. (1982), MOLECULAR CLONING; A LABORATORY MANUAL (Cold Spring Harbor Press, Cold Spring Harbor, N.Y.).
20 Yeast transformation by direct uptake may be carried out using the method of Hinnen et al. (1978) Proc. Natl. Acad. Sci. U.S.A. 75: 1929. Mammalian transformations by direct uptake may be conducted using the calcium phosphate precipitation method of Graham and Van der Eb (1978), Virology 52:546 or the various known modifications thereof.

Vector construction employs techniques which are known in the art. Site-specific
25 DNA cleavage is performed by treating with suitable restriction enzymes under conditions which generally are specified by the manufacturer of these commercially available enzymes. The cleaved fragments may be separated using polyacrylamide or agarose gel electrophoresis techniques, according to the general procedures found in Methods in Enzymology (1980) 65:499-560. Sticky ended cleavage fragments may be blunt ended
30 using E. coli DNA polymerase I (Klenow) in the presence of the appropriate

deoxynucleotide triphosphates (dNTPs) present in the mixture. Treatment with S1 nuclease may also be used, resulting in the hydrolysis of any single stranded DNA portions.

Ligations are carried out using standard buffer and temperature conditions using T4 DNA ligase and ATP; sticky end ligations require less ATP and less ligase than blunt end ligations. When vector fragments are used as part of a ligation mixture, the vector fragment is often treated with bacterial alkaline phosphatase (BAP) or calf intestinal alkaline phosphatase to remove the 5'-phosphate and thus prevent religation of the vector; alternatively, restriction enzyme digestion of unwanted fragments can be used to prevent ligation. Ligation mixtures are transformed into suitable cloning hosts, such as *E. coli*, and successful transformants selected by, for example, antibiotic resistance, and screened for the correct construction.

Synthetic oligonucleotides may be prepared using an automated oligonucleotide synthesizer as described by Warner (1984), DNA 3:401. If desired, the synthetic strands may be labeled with ^{32}P by treatment with polynucleotide kinase in the presence of ^{32}P -ATP, using standard conditions for the reaction. DNA sequences, including those isolated from cDNA libraries, may be modified by known techniques, including, for example site directed mutagenesis, as described by Zoller (1982), Nucleic Acids Res. 10:6487.

The expression constructs of the present invention, including the desired fusion, or individual expression constructs comprising the individual components of these fusions, may be used for nucleic acid immunization, to activate HCV-specific T cells, using standard gene delivery protocols. Methods for gene delivery are known in the art. See, e.g., U.S. Patent Nos. 5,399,346, 5,580,859, 5,589,466, incorporated by reference herein in their entireties. Genes can be delivered either directly to the vertebrate subject or, alternatively, delivered *ex vivo*, to cells derived from the subject and the cells reimplanted in the subject. For example, the constructs can be delivered as plasmid DNA, e.g., contained within a plasmid, such as pBR322, pUC, or ColE1

Additionally, the expression constructs can be packaged in liposomes prior to delivery to the cells. Lipid encapsulation is generally accomplished using liposomes which are able to stably bind or entrap and retain nucleic acid. The ratio of condensed DNA to lipid preparation can vary but will generally be around 1:1 (mg DNA:micromoles lipid), or

more of lipid. For a review of the use of liposomes as carriers for delivery of nucleic acids, see, Hug and Sleight, *Biochim. Biophys. Acta.* (1991) 1097:1-17; Straubinger et al., in *Methods of Enzymology* (1983), Vol. 101, pp. 512-527.

Liposomal preparations for use with the present invention include cationic
 5 (positively charged), anionic (negatively charged) and neutral preparations, with cationic liposomes particularly preferred. Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy]propyl]-N,N,N-triethylammonium (DOTMA) liposomes are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, NY. (See, also, Felgner et al., *Proc. Natl. Acad. Sci. USA* (1987) 84:7413-7416). Other commercially available
 10 lipids include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer). Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g., Szoka et al., *Proc. Natl. Acad. Sci. USA* (1978) 75:4194-4198; PCT Publication No. WO 90/11092 for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. The various liposome-nucleic
 15 acid complexes are prepared using methods known in the art. See, e.g., Straubinger et al., in *METHODS OF IMMUNOLOGY* (1983), Vol. 101, pp. 512-527; Szoka et al., *Proc. Natl. Acad. Sci. USA* (1978) 75:4194-4198; Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* (1979) 17:77; Deamer and Bangham, *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977)
 20 76:836; Fraley et al., *Proc. Natl. Acad. Sci. USA* (1979) 76:3348; Enoch and Strittmatter, *Proc. Natl. Acad. Sci. USA* (1979) 76:145; Fraley et al., *J. Biol. Chem.* (1980) 255:10431; Szoka and Papahadjopoulos, *Proc. Natl. Acad. Sci. USA* (1978) 75:145; and Schaefer-Ridder et al., *Science* (1982) 215:166.

The DNA can also be delivered in cochleate lipid compositions similar to those
 25 described by Papahadjopoulos et al., *Biochem. Biophys. Acta.* (1975) 394:483-491. See, also, U.S. Patent Nos. 4,663,161 and 4,871,488.

A number of viral based systems have been developed for gene transfer into mammalian cells. For example, retroviruses provide a convenient platform for gene delivery systems, such as murine sarcoma virus, mouse mammary tumor virus, Moloney
 30 murine leukemia virus, and Rous sarcoma virus. A selected gene can be inserted into a

vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to cells of the subject either *in vivo* or *ex vivo*. A number of retroviral systems have been described (U.S. Patent No. 5,219,740; Miller and Rosman, *BioTechniques* (1989) 7:980-990; Miller, A.D., *Human Gene Therapy* (1990) 1:5-14; Scarpa et al., *Virology* (1991) 180:849-852; Burns et al., *Proc. Natl. Acad. Sci. USA* (1993) 90:8033-8037; and Boris-Lawrie and Temin, *Cur. Opin. Genet. Develop.* (1993) 3:102-109. Briefly, retroviral gene delivery vehicles of the present invention may be readily constructed from a wide variety of retroviruses, including for example, B, C, and D type retroviruses as well as spumaviruses and lentiviruses such as FIV, HIV, HIV-1, HIV-2 and SIV (see RNA Tumor Viruses, Second Edition, Cold Spring Harbor Laboratory, 1985). Such retroviruses may be readily obtained from depositories or collections such as the American Type Culture Collection ("ATCC"; 10801 University Blvd., Manassas, VA 20110-2209), or isolated from known sources using commonly available techniques.

A number of adenovirus vectors have also been described, such as adenovirus Type 2 and Type 5 vectors. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham, *J. Virol.* (1986) 57:267-274; Bett et al., *J. Virol.* (1993) 67:5911-5921; Mittereder et al., *Human Gene Therapy* (1994) 5:717-729; Seth et al., *J. Virol.* (1994) 68:933-940; Barr et al., *Gene Therapy* (1994) 1:51-58; Berkner, K.L. *BioTechniques* (1988) 6:616-629; and Rich et al., *Human Gene Therapy* (1993) 4:461-476).

Molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al., *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et al., *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery.

Members of the Alphavirus genus, such as but not limited to vectors derived from the Sindbis and Semliki Forest viruses, VEE, will also find use as viral vectors for delivering the gene of interest. For a description of Sindbis-virus derived vectors useful for the practice of the instant methods, see, Dubensky et al., *J. Virol.* (1996) 70:508-519; and International Publication Nos. WO 95/07995 and WO 96/17072.

Other vectors can be used, including but not limited to simian virus 40, cytomegalovirus. Bacterial vectors, such as *Salmonella* ssp. *Yersinia enterocolitica*, *Shigella* spp., *Vibrio cholerae*, *Mycobacterium* strain BCG, and *Listeria monocytogenes* can be used. Minichromosomes such as MC and MC1, bacteriophages, cosmids (plasmids into which phage lambda *cos* sites have been inserted) and replicons (genetic elements that are capable of replication under their own control in a cell) can also be used.

The expression constructs may also be encapsulated, adsorbed to, or associated with, particulate carriers. Such carriers present multiple copies of a selected molecule to the immune system and promote trapping and retention of molecules in local lymph nodes. The particles can be phagocytosed by macrophages and can enhance antigen presentation through cytokine release. Examples of particulate carriers include those derived from polymethyl methacrylate polymers, as well as microparticles derived from poly(lactides) and poly(lactide-co-glycolides), known as PLG. See, e.g., Jeffery et al., *Pharm. Res.* (1993) 10:362-368; and McGee et al., *J. Microencap.* (1996).

A wide variety of other methods can be used to deliver the expression constructs to cells. Such methods include DEAE dextran-mediated transfection, calcium phosphate precipitation, polylysine- or polyornithine-mediated transfection, or precipitation using other insoluble inorganic salts, such as strontium phosphate, aluminum silicates including bentonite and kaolin, chromic oxide, magnesium silicate, talc, and the like. Other useful methods of transfection include electroporation, sonoporation, protoplast fusion, liposomes, peptoid delivery, or microinjection. See, e.g., Sambrook et al., *supra*, for a discussion of techniques for transforming cells of interest; and Felgner, P.L., *Advanced Drug Delivery Reviews* (1990) 5:163-187, for a review of delivery systems useful for gene transfer. One particularly effective method of delivering DNA using electroporation is described in International Publication No. WO/0045823.

Additionally, biolistic delivery systems employing particulate carriers such as gold and tungsten, are especially useful for delivering the expression constructs of the present invention. The particles are coated with the construct to be delivered and accelerated to high velocity, generally under a reduced atmosphere, using a gun powder discharge from a "gene gun." For a description of such techniques, and apparatuses useful therefore, see,

e.g., U.S. Patent Nos. 4,945,050; 5,036,006; 5,100,792; 5,179,022; 5,371,015; and 5,478,744.

Compositions

5 The invention also provides compositions comprising the HCV polypeptides or polynucleotides described herein. Such compositions are useful as diagnostics, for example, using the mutant polypeptides (or polynucleotides encoding these polypeptides) in diagnostic reagents. Diagnostics using polypeptides and polynucleotides are known to those of skill in the art.

10 In addition, immunogenic compounds can be prepared from one or more immunogenic polypeptides derived from the polypeptides described herein, for example the ΔNS35 polypeptide. The preparation of immunogenic compounds which contain immunogenic polypeptide(s) as active ingredients is known to one skilled in the art. Typically, such immunogenic compounds are prepared as injectables, either as liquid
15 solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified, or the protein encapsulated in liposomes.

 Immunogenic and diagnostic compositions of the invention preferably comprise a pharmaceutically acceptable carrier. The carrier should not itself induce the production of
20 antibodies harmful to the host. Pharmaceutically acceptable carriers are well known to those in the art. Such carriers include, but are not limited to, large, slowly metabolized, macromolecules, such as proteins, polysaccharides such as latex functionalized sepharose, agarose, cellulose, cellulose beads and the like, polylactic acids, polyglycolic acids, polymeric amino acids such as polyglutamic acid, polylysine, and the like, amino acid
25 copolymers, and inactive virus particles.

 Pharmaceutically acceptable salts can also be used in compositions of the invention, for example, mineral salts such as hydrochlorides, hydrobromides, phosphates, or sulfates, as well as salts of organic acids such as acetates, proprionates, malonates, or benzoates. Especially useful protein substrates are serum albumins, keyhole limpet
30 hemocyanin, immunoglobulin molecules, thyroglobulin, ovalbumin, tetanus toxoid, and

other proteins well known to those of skill in the art. Compositions of the invention can also contain liquids or excipients, such as water, saline, glycerol, dextrose, ethanol, or the like, singly or in combination, as well as substances such as wetting agents, emulsifying agents, or pH buffering agents. Liposomes can also be used as a carrier for a composition of the invention, such liposomes are described above.

If desired, co-stimulatory molecules which improve immunogen presentation to lymphocytes, such as B7-1 or B7-2, or cytokines such as GM-CSF, IL-2, and IL-12, can be included in a composition of the invention. Optionally, adjuvants can also be included in a composition. Adjuvants which can be used include, but are not limited to: (1) aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, aluminum sulfate, etc; (2) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59 (PCT Publ. No. WO 90/14837), containing 5% Squalene, 0.5% Tween 80, and 0.5% Span 85 (optionally containing various amounts of MTP-PE), formulated into submicron particles using a microfluidizer such as Model 110Y microfluidizer (Microfluidics, Newton, MA), (b) SAF, containing 10% Squalene, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP (see below) either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) RibiTM adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (DetoxTM); (3) saponin adjuvants, such as StimulonTM (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes); (4) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (5) cytokines, such as interleukins (e.g., IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (e.g., gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), *etc.*; (6) detoxified mutants of a bacterial ADP-ribosylating toxin such as a cholera toxin (CT), a pertussis toxin (PT), or an *E. coli* heat-labile toxin (LT), particularly LT-K63, LT-R72, CT-S109, PT-K9/G129; see, e.g., WO 93/13302 and WO 92/19265; (7) other

substances that act as immunostimulating agents to enhance the effectiveness of the composition; and (8) microparticles with adsorbed macromolecules, as described in copending U.S. Patent Application Serial No. 09/285,855 (filed April 2, 1999) and international Patent Application Serial No. PCT/US99/17308 (filed July 29, 1999). Alum and MF59 are preferred. The effectiveness of an adjuvant can be determined by measuring the amount of antibodies directed against an immunogenic polypeptide containing an HCV antigenic sequence resulting from administration of this polypeptide in immunogenic compounds which are also comprised of the various adjuvants.

As mentioned above, muramyl peptides include, but are not limited to, N-acetylmuramyl-L-threonyl-D-isoglutamine (thr-MDP), -acetyl-normuramyl-L-alanyl-D-isoglutamine (CGP 11637, referred to as nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine (CGP 19835A, referred to as MTP-PE), *etc.*

Thus, such recombinant or synthetic HCV polypeptides can be used in vaccines and as diagnostics. Further, antibodies raised against these polypeptides can also be used as diagnostics, or for passive immunotherapy. In addition, antibodies to these polypeptides are useful for isolating and identifying HCV particles.

Native HCV antigens can also be isolated from HCV virions. The virions can be grown in HCV infected cells in tissue culture, or in an infected host.

Administration and Delivery

The polynucleotide and polypeptide compositions described herein (*e.g.*, immunogenic compounds) may be administered to a subject using any suitable delivery means. Methods of delivering nucleic acids into host cells are discussed above. Further, HCV polynucleotides and/or polypeptides can be administered parenterally, by injection, usually, subcutaneously, intramuscularly, transdermally or transcutaneously. Certain adjuvants, *e.g.* LTK63, LTR72 or PLG formulations, can be administered intranasally or orally. Additional formulations which are suitable for other modes of administration include suppositories. For suppositories, traditional binders and carriers can include, for example, polyalkylene glycols or triglycerides; such suppositories can be formed from

mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%. Other oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10%-95% of active ingredient, preferably 25%-70%.

The polypeptides of the present invention can be formulated into the immunogenic compound as neutral or salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with free amino groups of the peptide) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids such as acetic, oxalic, tartaric, maleic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

The immunogenic compounds are administered in a manner compatible with the dosage formulation, and in such amount as will be prophylactically and/or therapeutically effective. The quantity to be administered, which is generally in the range of 5 micrograms to 250 micrograms of polypeptide per dose, depends on the subject to be treated, capacity of the subject's immune system to synthesize antibodies, and the degree of protection desired. Precise amounts of active ingredient required to be administered may depend on the judgment of the practitioner and can be peculiar to each subject.

The immunogenic compound can be given in a single dose schedule, or preferably in a multiple dose schedule. A multiple dose schedule is one in which a primary course of vaccination can be with 1-10 separate doses, followed by other doses given at subsequent time intervals required to maintain and or reenforce the immune response, for example, at 1-4 months for a second dose, and if needed, a subsequent dose(s) after several months. Further, the course of administration may include polynucleotides and polypeptides, together or sequentially (for example, priming with a polynucleotide composition and boosting with a polypeptide composition). The dosage regimen will also, at least in part,

be determined by the need of the individual and be dependent upon the judgment of the practitioner.

In certain embodiments, administration of the polynucleotides and polypeptides described herein is used to activate T cells. In addition to the practical advantages of simplicity of construction and modification, administration of polynucleotides encoding mutant NS polypeptides results in the synthesis of a mutant NS polypeptide in the host. Thus, these immunogens are presented to the host immune system with native post-translational modifications, structure, and conformation. The polynucleotides are preferably injected intramuscularly to a large mammal, such as a human, at a dose of 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 5 or 10 mg/kg.

The proteins and/or polynucleotides can be administered either to a mammal which is not infected with an HCV or can be administered to an HCV-infected mammal. The particular dosages of the polynucleotides or fusion proteins in a composition or will depend on many factors including, but not limited to the species, age, and general condition of the mammal to which the composition is administered, and the mode of administration of the composition. An effective amount of the composition of the invention can be readily determined using only routine experimentation. *In vitro* and *in vivo* models can be employed to identify appropriate doses. Generally, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 5 or 10 mg will be administered to a large mammal, such as a baboon, chimpanzee, or human. If desired, co-stimulatory molecules or adjuvants can also be provided before, after, or together with the compositions.

Antibodies and Diagnostics

Antibodies, both monoclonal and polyclonal, which are directed against HCV epitopes are particularly useful in diagnosis, and those which are neutralizing are useful in passive immunotherapy. Monoclonal antibodies, in particular, may be used to raise anti-idiotypic antibodies.

Anti-idiotypic antibodies are immunoglobulins which carry an "internal image" of the antigen of the infectious agent against which protection is desired. Techniques for raising anti-idiotypic antibodies are known in the art. See, e.g., Grzych (1985), Nature

316:74; MacNamara et al. (1984), Science 226:1325, Uytdehaag et al (1985), J. Immunol. 134:1225. These anti-idiotypic antibodies may also be useful for treatment and/or diagnosis of NANBH, as well as for an elucidation of the immunogenic regions of HCV antigens.

An immunoassay for viral antigen may use, for example, a monoclonal antibody
5 directed towards a viral epitope, a combination of monoclonal antibodies directed towards epitopes of one viral polypeptide, monoclonal antibodies directed towards epitopes of different viral polypeptides, polyclonal antibodies directed towards the same viral antigen, polyclonal antibodies directed towards different viral antigens or a combination of monoclonal and polyclonal antibodies.

10 Immunoassay protocols may be based, for example, upon competition, or direct reaction, or sandwich type assays. Protocols may also, for example, use solid supports, or may be by immunoprecipitation. Most assays involve the use of labeled antibody or polypeptide. The labels may be, for example, fluorescent, chemiluminescent, radioactive, or dye molecules. Assays which amplify the signals from the probe are also known.

15 Examples of which are assays which utilize biotin and avidin, and enzyme-labeled and mediated immunoassays, such as ELISA assays.

An enzyme-linked immunosorbent assay (ELISA) can be used to measure either antigen or antibody concentrations. This method depends upon conjugation of an enzyme to either an antigen or an antibody, and uses the bound enzyme activity as a quantitative
20 label. To measure antibody, the known antigen is fixed to a solid phase (e.g., a microplate or plastic cup), incubated with test serum dilutions, washed, incubated with anti-immunoglobulin labeled with an enzyme, and washed again. Enzymes suitable for labeling are known in the art, and include, for example, horseradish peroxidase. Enzyme activity bound to the solid phase is measured by adding the specific substrate, and determining
25 product formation or substrate utilization colorimetrically. The enzyme activity bound is a direct function of the amount of antibody bound.

To measure antigen, a known specific antibody is fixed to the solid phase, the test material containing antigen is added, after an incubation the solid phase is washed, and a second enzyme-labeled antibody is added. After washing, substrate is added, and enzyme
30 activity is estimated colorimetrically, and related to antigen concentration.

The HCV fusion proteins, such as NS3 mutant and core fusion proteins, can also be used to produce HCV-specific polyclonal and monoclonal antibodies. HCV-specific polyclonal and monoclonal antibodies specifically bind to HCV antigens.

5 Polyclonal antibodies can be produced by administering the fusion protein to a mammal, such as a mouse, a rabbit, a goat, or a horse. Serum from the immunized animal is collected and the antibodies are purified from the plasma by, for example, precipitation with ammonium sulfate, followed by chromatography, preferably affinity chromatography. Techniques for producing and processing polyclonal antisera are known in the art.

10 Monoclonal antibodies directed against HCV-specific epitopes present in the fusion proteins can also be readily produced. Normal B cells from a mammal, such as a mouse, immunized with, e.g., a mutant NS3 polypeptide or NS-core fusion protein can be fused with, for example, HAT-sensitive mouse myeloma cells to produce hybridomas. Hybridomas producing HCV-specific antibodies can be identified using RIA or ELISA and isolated by cloning in semi-solid agar or by limiting dilution. Clones producing HCV-
15 specific antibodies are isolated by another round of screening.

Antibodies, either monoclonal and polyclonal, which are directed against HCV epitopes, are particularly useful for detecting the presence of HCV or HCV antigens in a sample, such as a serum sample from an HCV-infected human. An immunoassay for an HCV antigen may utilize one antibody or several antibodies. An immunoassay for an
20 HCV antigen may use, for example, a monoclonal antibody directed towards an HCV epitope, a combination of monoclonal antibodies directed towards epitopes of one HCV polypeptide, monoclonal antibodies directed towards epitopes of different HCV polypeptides, polyclonal antibodies directed towards the same HCV antigen, polyclonal antibodies directed towards different HCV antigens, or a combination of monoclonal and
25 polyclonal antibodies. Immunoassay protocols may be based, for example, upon competition, direct reaction, or sandwich type assays using, for example, labeled antibody. The labels may be, for example, fluorescent, chemiluminescent, or radioactive.

The polyclonal or monoclonal antibodies may further be used to isolate HCV particles or antigens by immunoaffinity columns. The antibodies can be affixed to a solid
30 support by, for example, adsorption or by covalent linkage so that the antibodies retain

their immunoselective activity. Optionally, spacer groups may be included so that the antigen binding site of the antibody remains accessible. The immobilized antibodies can then be used to bind HCV particles or antigens from a biological sample, such as blood or plasma. The bound HCV particles or antigens are recovered from the column matrix by, for example, a change in pH.

Methods of Eliciting Immune Responses

HCV-specific T cells that are activated by the above-described polypeptides, expressed *in vivo* or *in vitro* preferably recognize an epitope of an HCV polypeptide such as a mutant NS3 polypeptide, including an epitope of a mutant HCV polypeptide. HCV-specific T cells can be CD8⁺ or CD4⁺.

HCV-specific CD8⁺ T cells preferably are cytotoxic T lymphocytes (CTL) which can kill HCV-infected cells that display NS3, NS4, NS5a, NS5b epitopes complexed with an MHC class I molecule. HCV-specific CD8⁺ T cells may also express interferon- γ (IFN- γ). HCV-specific CD8⁺ T cells can be detected by, for example, ⁵¹Cr release assays. ⁵¹Cr release assays measure the ability of HCV-specific CD8⁺ T cells to lyse target cells displaying a nonstructural (*e.g.*, mutant NS) epitope. HCV-specific CD8⁺ T cells which express IFN- γ can also be detected by immunological methods, preferably by intracellular staining for IFN- γ after *in vitro* stimulation with a mutant NS polypeptide.

HCV-specific CD4⁺ cells activated by the above-described polypeptides, expressed *in vivo* or *in vitro*, and combinations of the individual components of these proteins, preferably recognize an epitope of a mutant non-structural polypeptide, including an epitope of a mutant protein, that is bound to an MHC class II molecule on an HCV-infected cell and proliferate in response to stimulating mutant peptides.

HCV-specific CD4⁺ T cells can be detected by a lymphoproliferation assay. Lymphoproliferation assays measure the ability of HCV-specific CD4⁺ T cells to proliferate in response to an epitope.

Mutant NS (or fusions thereof with core, envelope or other viral polypeptides) can be used to activate HCV-specific T cells either *in vitro* or *in vivo*. Activation of HCV-specific T cells can be used, *inter alia*, to provide model systems to optimize CTL

responses to HCV and to provide prophylactic or therapeutic treatment against HCV infection. For *in vitro* activation, proteins are preferably supplied to T cells via a plasmid or a viral vector, such as an adenovirus vector, as described above.

5 Polyclonal populations of T cells can be derived from the blood, and preferably from peripheral lymphoid organs, such as lymph nodes, spleen, or thymus, of mammals that have been infected with an HCV. Preferred mammals include mice, chimpanzees, baboons, and humans. The HCV serves to expand the number of activated HCV-specific T cells in the mammal. The HCV-specific T cells derived from the mammal can then be restimulated *in vitro* by adding HCV epitopic peptides to the T cells. The HCV-specific T
10 cells can then be tested for, *inter alia*, proliferation (*e.g.*, lymphoproliferation assays known in the art), the production of IFN- γ , and the ability to lyse target cells displaying HCV NS epitopes *in vitro*.

The following examples are meant to illustrate the invention and are not meant to
15 limit it in any way. Those of ordinary skill in the art will recognize modifications within the spirit and scope of the invention as set forth herein.

EXAMPLES

Example 1: Constructs

pCMV-II: pCMV-II (Figure 7, SEQ ID NO:5) was created to contain the human
5 CMV promoter, enhancer, intron A, polylinker and the bovine growth hormone terminator
in a deleted-pUC backbone (Life Technologies).

pT7-HCV: pT7-HCV was created in a polylinker-modified pUC vector to contain
full-length HCV cDNA preceded by a synthetic T7 promoter. pT7-HCV also contains the
complete 5' UTR and the poly A version of the 3' UTR.

10 pCMV.ΔNS35: To generate pCMV.ΔNS35 (Figure 5, SEQ ID NO:3), a two step
procedure was undertaken. First, a PCR product was generated from pT7-HCV that
corresponded to the following: a 5' EcoRI site, followed by the Kozak sequence of
ACCATGG; the initiator ATG followed by amino acid #1242 and continuing to the StuI
site. Second, the StuI to XbaI fragment from a full-length genomic clone was isolated.
15 The genomic clone consisted of the T7 promoter fused to the full-length HCV cDNA with
the poly A version of the 3' end, in a pUC vector. Finally, the EcoRI-StuI and StuI-XbaI
fragments were ligated into the pCMV-II expression vector, transformed into HB101
competent cells and plated onto ampicillin (100 µg/ml). Miniprep analyses led to the
identification of the desired clone which was amplified on a larger scale using a Quigen
20 Gigaprep kit following the manufacturer's specifications. The resulting clone was named
pCMV.ΔNS35 (Figure 5, SEQ ID NO:3).

pd.ΔNS3NS5: As shown schematically in Figure 10, the yeast expression plasmid
pd.ΔNS3NS5 (SEQ ID NO:8) was constructed using restriction fragments obtained from
the mammalian expression plasmid pCMV.KM.ΔNS35. pCMV.KM.ΔNS35 is identical to
25 pCMV.ΔNS35 (Figure 5, SEQ ID NO:3) except that it contains a kanamycin resistance
gene in the viral backbone. pCMV.KM.ΔNS35 was digested with EcoRI and NheI to
obtain 2895bp EcoRI-NheI fragment. EcoRI-NheI fragment was ligated into pRSET
HindIII-NheI subcloning vector with oligos (HE) from HindIII to EcoRI. After sequence
verification, pRSETHindIII-NheI #6 was digested with HindIII and NheI to obtain a

2908bp HindIII-NheI fragment.

pCMV.KM.ΔNS35 was linearized with XbaI and ligated with synthetic oligos (XS) from XbaI-SalI. The ligation was digested with NheI and SalI to obtain 2481bp NheI-SalI fragment. The fragment was ligated into pET3a NheI-SalI subcloning vector. After
5 sequence verification, pET3a NheI-SalI #2 was digested with NheI and SalI to obtain a 2481bp NheI-SalI fragment. BamHI-HindIII ADH2/GAPDH promoter fragment was then ligated with HindIII-NheI and NheI-SalI fragments into pBS24.1 BamHI-SalI yeast expression vector.

pd.ΔNS3NS5.PJ: pd.ΔNS3NS5.PJ (Figures 13 and 14; SEQ ID NO:10) was
10 generated to create a "perfect junction" at the 5' and 3' end of the HCV coding region. At the 5' end of pd.ΔNS3NS5, there were 6 extra bases between the yeast ADH2/GAPDH promoter and the ATG of the polypeptide. At the 3' end, there were 52 bases of untranslated sequence between the stop codon of the polypeptide and the α-factor terminator in the yeast expression vector. pd.ΔNS3NS5.PJ was created by digesting
15 pd.ΔNS3NS5 #17 with ScaI and SphI to obtain 4963bp ScaI-SphI fragment. pd.NS5b3011 was digested with SphI and SalI to obtain a 321bp SphI-SalI fragment which gave the "perfect junction" at the 3' end of the polypeptide. The ScaI-SphI and SphI-SalI fragments were ligated into pSP72 HindIII-SalI subcloning vector with synthetic oligos from HindIII-ScaI(HS) for the "perfect junction" at the 5' end.

20 The region of synthetic sequence in pSP72 HindIII-SalI clone# 6 was verified. pSP72 HindIII-SalI clone#6 was digested with HindIII and BlnI or with BlnI and SalI to obtain 2441bp HindIII-BlnI and 2895bp BlnI-SalI fragments, respectively. The BamHI-HindIII ADH2/GAPDH promoter fragment was ligated to HindIII-BlnI and BlnI-SalI fragments into pBS24.1 BamHI-SalI yeast expression vector.

25 pd.ΔNS3NS5.PJ.core121RT and pd.ΔNS3NS5.PJ.core173RT were generated and encode HCV core aa 1-121 at the C-terminus of the ΔNS3NS5 polypeptide (designated pd.ΔNS3NS5.PJ.core121RT, SEQ ID NO:12) and core aa 1-173 at the C-terminus of the ΔNS3NS5 polypeptide (designated pd.ΔNS3NS5.PJ.core173RT, SEQ ID NO:14). The core sequence had aa 9 mutated from Lys to Arg and aa 11 mutated from Asn to Thr,

designated as core 121RT or 173RT.

5 pd.ΔNS3NS5.PJ.core121RT and pd.ΔNS3NS5.PJ.core173RT: To generate
pd.ΔNS3NS5.PJ.core121RT (Figure 17, SEQ ID NO:12) and pd.ΔNS3NS5.PJ.core173RT
(Figure 18, SEQ ID NO:14). As shown in Figure 16, a NotI-SalI HCVcore121RT and
10 HCVcore173RT were amplified by PCR, from an *E. coli* expression plasmid,
pSODCF2.HCVcore191RT #2. Either the core 121RT Not-SalI PCR product or the core
173RT Not-SalI PCR product were ligated into a pT7Blue2 PstI-SalI subcloning vector
with synthetic oligos (PN) from PstI to NotI. After sequence confirmation,
pT7Blue2core121RT clone#9 and pT7Blue2core173RT clone#11 was digested with PstI
15 and SalI to obtain 403bp and 559bp PstI-SalI fragments, respectively, for further cloning.

A 121bp NotI-PstI fragment from pSP72 HindIII-SalI clone #6 was isolated as
described above during the cloning of pd.ΔNS3NS5.PJ. NotI-PstI and PstI-SalI fragments
were assembled into a vector made by digesting pd.ΔNS3NS5.PJ clone#5 (described above)
with NotI and SalI.

15 ΔNS3NS5 and Core 140 and Core 150: An HCV core epitope was found which
elicits CTLs in baboons (HCV core aa 121-135). Since pd.ΔNS3NS5.PJ.core121RT ends
right before this potentially important epitope and was expressed better than the longer
pd.ΔNS3NS5.PJ.core173RT construct (Example 2), two intermediate constructs were
made which include this epitope, possibly giving intermediate expression levels. The two
20 new constructs fused HCV core aa 1-140 or HCV core aa1-150 to the C terminus of
ΔNS3NS5.PJ.

25 pd.ΔNS3NS5.PJ.core140RT (Figure 21, SEQ ID NO:16) and
pd.ΔNS3NS5.PJ.core150RT (Figure 22, SEQ ID NO:18): As shown in Figure 20, a PstI-
SalI HCVcore140RT and a PstI-SalIHCVcore150RT fragment were amplified by PCR
from pd.ΔNS3NS5.PJ.core173RT clone #16. Ligate either HCV core PstI-SalI PCR
products into pT7Blue2 PstI-SalI subcloning vector. After sequence confirmation,
pT7Blue2core140RT clone#22 and pT7Blue2core150RT clone#26 were digested with
PstI-SalI to obtain 460bp and 490bp PstI-SalI fragments, respectively, for further cloning.

A 121bp NotI-PstI fragment was isolated from pSP72 HindIII-SalI clone #6 (as described above during the cloning of pd.ΔNS3NS5.PJ. NotI-PstI and PstI-SalI fragments were assembled into a vector made by digesting pd.ΔNS3NS5.PJ clone#5 (described above) with NotI and SalI.

5

Example 2: Protein Expression

Various of the constructs described herein, encoding HCV-1 ΔNS3 to NS5 antigen (aa 1242-3011), were expressed in yeast. *S. cerevisiae* strain AD3 was transformed with pd.ΔNS3NS5 and checked for expression. A stained protein band at the expected molecular weight of 194 kD was not observed (Figure 12). Strain AD3 was also transformed with pd.ΔNS3NS5.PJ clone #5 and checked for expression. A protein band of the expected molecular weight of 194kD was detected (Figure 15). Strain AD3 was transformed with pd.ΔNS3NS5.PJ.core121RT clone #6 and pd.ΔNS3NS5.PJ.core173RT clone#15 and checked for expression. Protein bands of the expected molecular weight of 206kD and 210kD, respectively, were observed. Expression levels of the pd.ΔNS3NS5.PJ.core173RT construct were much less than that of the pd.ΔNS3NS5.PJ.core121RT construct. (See Figure19). Thus, there is a correlation of protein expression levels and the length of HCV core.

Strain AD3 were transformed with pd.ΔNS3NS5.PJ.core140RT clone# 29 and pd.ΔNS3NS5.PJ.core150RT clone#35 and checked for expression. Bands of the expected molecular weights of 208kD and 209kD were seen by stain at levels close to those of pd.ΔNS3NS5core173RT (Figure 23).

Example 3: Eliciting Immune Responses

A. Immunization

To evaluate the immunogenicity of the mutant NS polypeptides, studies using guinea pigs, rabbits, mice, rhesus macaques and/or baboons are performed. The studies are structured as follows: DNA immunization alone (single or multiple); DNA immunization followed by protein immunization (boost); DNA immunization followed by protein

immunization; immunization by PLG particles. Immunization is intramuscular or mucosally.

B. Humoral Immune Response

5 The humoral immune response is checked in serum specimens from immunized animals with anti-NS antibody ELISAs (enzyme-linked immunosorbent assays) at various times post-immunization. Briefly, serum from immunized animals is screened for antibodies directed against the NS or mutant NS proteins. Wells of ELISA microtiter plates are coated overnight with the selected HCV protein and washed four times; subsequently, blocking is done with PBS-0.2% Tween (Sigma). After removal of the blocking solution, diluted mouse serum is added. Sera are tested at various dilutions. Microtiter plates are washed and incubated with a secondary, peroxidase-coupled anti-mouse IgG antibody (Pierce, Rockford, IL). ELISA plates are washed and 3, 3', 5, 5'-tetramethyl benzidine (TMB; Pierce) is added per well. The optical density of each well is measured. Titers are typically reported as the reciprocal of the dilution of serum that gave a half-maximum optical density (O.D.). Similarly, generation of neutralization of binding (NOB) antibodies can be measured by methods known in the art.

C. Cellular Immune Response

20 The frequency of specific cytotoxic T-lymphocytes (CTL) is evaluated by a standard chromium release assay of peptide pulsed Balb/c mouse CD4 cells. Briefly, spleen cells (Effector cells, E) are obtained from the BALB/c mice immunized, cultured, restimulated, and assayed for CTL activity against HCV peptide-pulsed target cells. Cytotoxic activity is measured in a standard ⁵¹Cr release assay.

25

Example 4: Immunization with PLG-delivered DNA.

 The polylactide-co-glycolide (PLG) polymers are obtained from Boehringer Ingelheim, U.S.A. The PLG polymer is RG505, which has a copolymer ratio of 50/50 and a molecular weight of 65 kDa (manufacturers data). Cationic microparticles with adsorbed DNA are prepared using a modified solvent evaporation process, essentially as described in

30

Singh et al., *Proc. Natl. Acad. Sci. USA* (2000) 97:811-816. Briefly, the microparticles are prepared by emulsifying a 5% w/v polymer solution in methylene chloride with PBS at high speed using an IKA homogenizer. The primary emulsion is then added to distilled water containing cetyl trimethyl ammonium bromide (CTAB) (0.5% w/v). This results in the formation of a w/o/w emulsion which was stirred at room temperature, allowing the methylene chloride to evaporate. The resulting microparticles are washed in distilled water by centrifugation and freeze dried. Following preparation, washing and collection, DNA is adsorbed onto the microparticles by incubating cationic microparticles in a solution of DNA. The microparticles are then separated by centrifugation, the pellet washed with TE buffer and the microparticles are freeze dried, resuspended and administered to animals. Antibody titers are measured by ELISA assays.

All patents, patent applications, and other publications mentioned herein, are hereby incorporated herein by reference in their entireties.

What is claimed is:

1. An isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a mutation in the catalytic domain of NS3, wherein said mutation functionally disrupts the catalytic domain.
- 5 2. The polypeptide of claim 1, wherein the mutation comprises a deletion.
3. The polypeptide of claim 1, wherein the mutation comprises a substitution.
- 10 4. The polypeptide of claim 1, wherein said NS polypeptide comprises NS3, NS4 and NS5.
5. The polypeptide of claim 1, wherein said NS polypeptide consists of NS3, NS4 and NS5.
- 15 6. The polypeptide of claim 1, wherein said NS polypeptide consists of NS3 and NS5.
7. The polypeptide of claim 6, wherein NS5 consists of NS5a.
- 20 8. The polypeptide of claim 6, wherein NS5 consists of NS5b.
9. The polypeptide of claim 1, wherein said NS polypeptide consists of NS3 and NS4.
- 25 10. The polypeptide of claim 9, wherein NS4 consists of NS4a.
11. The polypeptide of claim 9, wherein NS4 consists of NS4b.

12. The polypeptide of claim 4, further comprising a second viral polypeptide that is not NS3, NS4, or NS5 of HCV.

5 13. The polypeptide of claim 12, wherein the second viral polypeptide comprises an HCV Core polypeptide ("C"), or fragment thereof.

14. The polypeptide of claim 13, wherein the C polypeptide is truncated.

10 15. The polypeptide of claim 14, wherein the truncation is at amino acid 121.

16. The polypeptide of claim 12, wherein the polypeptide further comprises an HCV envelope protein ("E").

15 17. The polypeptide of claim 16, wherein the E is E1.

18. The polypeptide of claim 16, wherein the E is E2.

20 19. A composition comprising
(a) the polypeptide of claim 1; and
(b) a pharmaceutically acceptable excipient.

20. An isolated and purified polynucleotide which encodes the mutant HCV polypeptide according to claim 1.

25 21. A composition comprising
(a) the isolated purified polynucleotide of claim 20; and
(b) a pharmaceutically acceptable excipient.

30 22. The composition of claim 21, wherein the polynucleotide is DNA.

23. The composition of claim 21, wherein the polynucleotide is in a plasmid.
24. An expression vector comprising the polynucleotide of claim 20.
- 5 25. An expression vector comprising the polynucleotide of SEQ ID NO:8.
26. A host cell comprising the polynucleotide of claim 20.
27. The host cell of claim 26, wherein the cell is a yeast cell.
- 10 28. The host cell of claim 26, wherein the cell is a mammalian cell.
29. The host cell of claim 26, wherein the cell is an insect cell.
- 15 30. The host cell of claim 26, wherein the cell is a plant cell.
31. The host cell of claim 26, wherein the polynucleotide comprises the sequence of SEQ ID NO:8.
- 20 32. The polypeptide of claim 1, wherein the polypeptide further comprises SEQ ID NO:9.
33. A method of preparing a mutant NS HCV polypeptide, wherein the method comprises the steps of:
 - 25 a. transforming a host cell with an expression vector according to claim 24, under conditions wherein the polypeptide is expressed; and
 - 30 b. isolating the polypeptide.

34. The method of claim 33, wherein the host cell is a yeast cell.
35. The method of claim 33, wherein the host cell is a mammalian cell.
- 5 36. The method of claim 33, wherein the host cell is an insect cell.
37. The method of claim 33, wherein the host cell is a plant cell.
38. An antibody that specifically binds to a polypeptide of claim 1.
- 10 39. The antibody of claim 38, wherein the antibody is a monoclonal antibody.
40. The antibody of claim 38, wherein the antibody is a purified polyclonal antibody.
- 15 41. A method of eliciting an immune response in a subject, comprising the step of administering to the subject a polypeptide of claim 1.
42. A method of eliciting an immune response in a subject, comprising the step of administering to the subject a polynucleotide of claim 20.
- 20

ABSTRACT

Polypeptides comprising a mutant non-structural Hepatitis C virus useful in diagnostic and/or immunogenic compositions are disclosed, in which the mutant is an N-terminal mutation that functionally disrupt the catalytic domain of NS3. Polynucleotides encoding these polypeptides, host cells transformed with polynucleotides and methods of using the polypeptides and polynucleotides are also disclosed.

Cloning Scheme for Generating pCMV-NS35

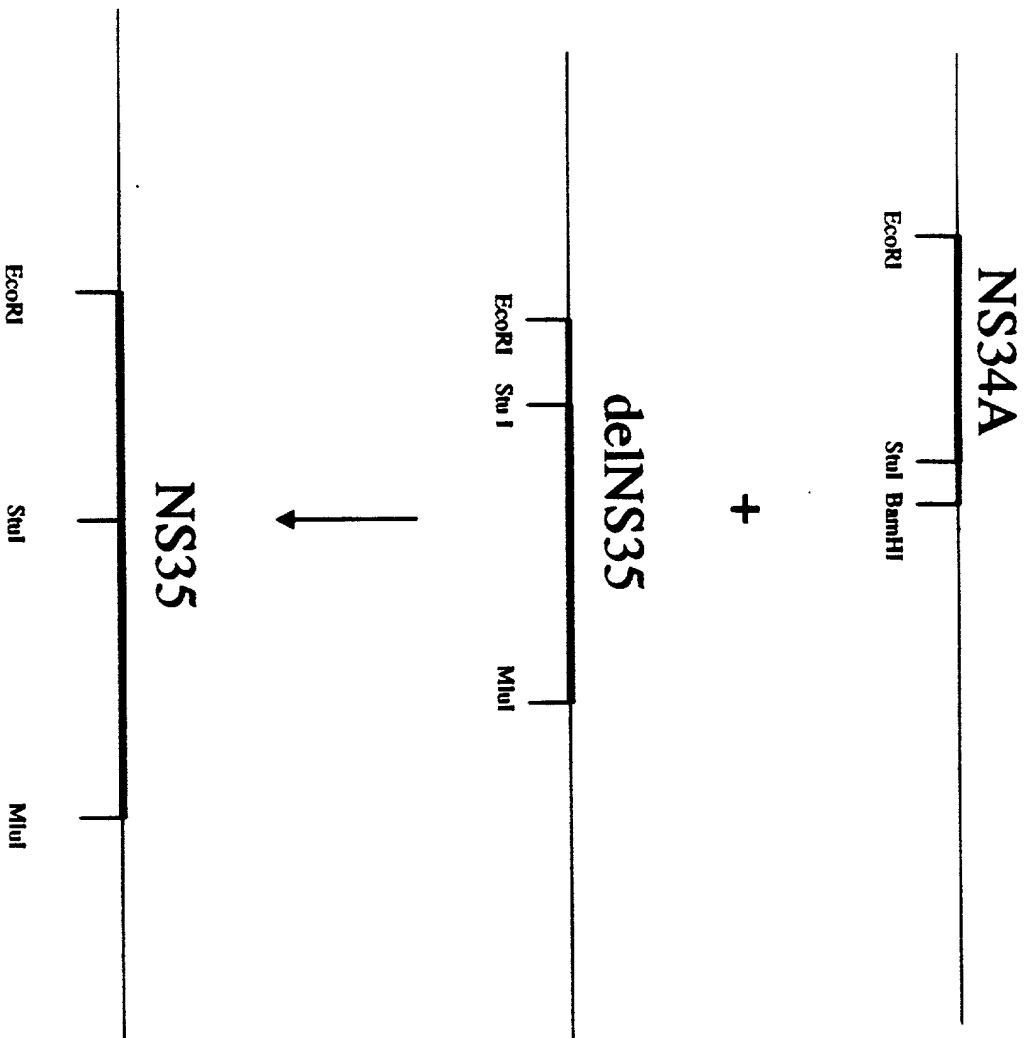
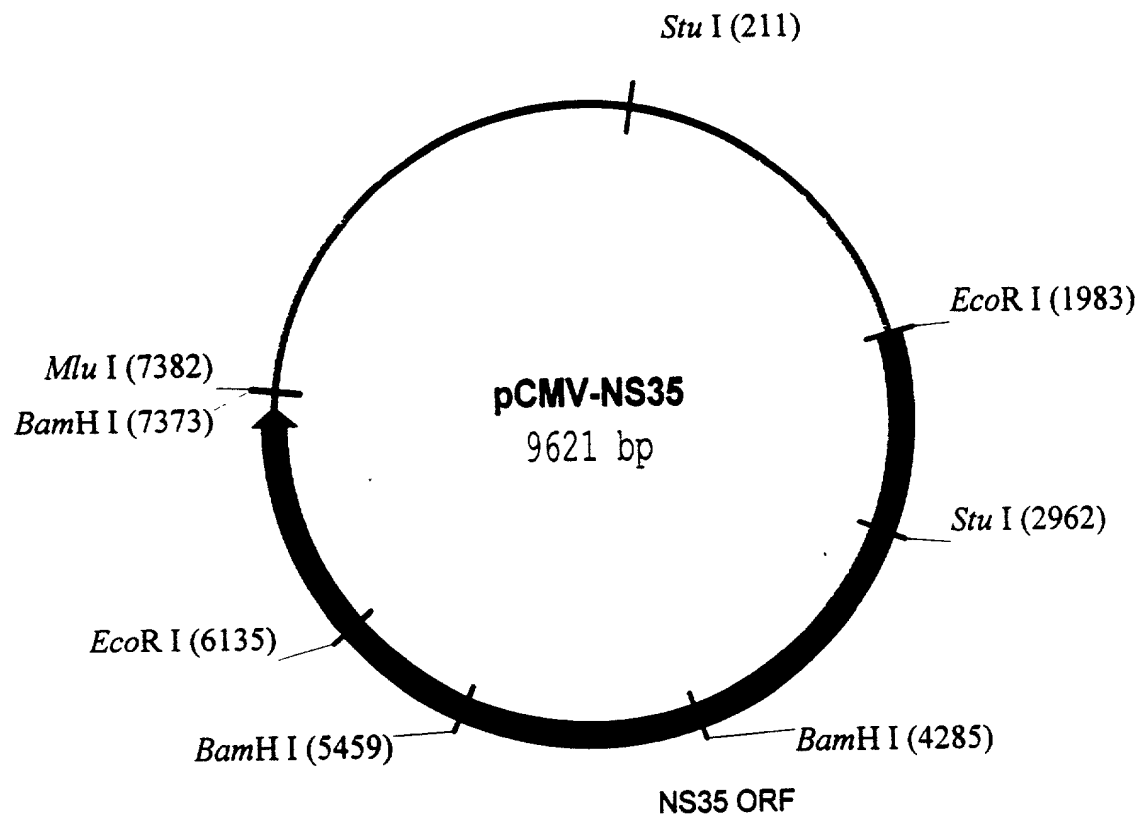


FIGURE 1

FIGURE 2



002217 547260

1	TCGCGCGTTT AGCGCGCAAA	CGGTGATGAC GCCACTACTG	GGTGAAAACC CCACTTTTGG	TCTGACACAT AGACTGTGTA	GCAGCTCCCG CGTCGAGGGC	GAGACGGTCA CTCTGCCAGT	CAGCTTGTCT GTGCAACAGA	GTAAGCGGAT CATTGCGCTA
81	GCCGGGAGCA CGGCCCTCGT	GACAAGCCCG CTGTTCCGGC	TCAGGGCGCG AGTCCCGCGC	TCAGCGGGTG AGTCGCCAC	TTGGCGGGTG AACC GCCAC	TCGGGGCTGG AGCCCCGACC	CTTAACATG GAATTGATAC	CGGCATCAGA GCCGTAGTCT
					StuI ~~~~~			
161	GCAGATTGTA CGTCTAACAT	CTGAGAGTGC GACTCTCACG	ACCATATGAA TGTATACTT	GCTTTTTGCA CGAAAAACGT	AAAGCCTAGG TTTCGGATCC	CCTCCAAAAA GGAGGTTTTT	AGCCTCCTCA TCGGAGGAGT	CTACTTCTGG GATGAAGAC
241	AATAGCTCAG TTATCGAGTC	AGGCCGAGGC TCCGGCTCCG	GGCCTCGGCC CCGGAGCCGG	TCTGCATAAA AGACGTATTT	TAAAAAAAAT ATTTTTTTTA	TAGTCAGCCA ATCAGTCGGT	TGGGGCGGAG ACCCCGCCTC	AATGGGCGGA TTACCCGCCT
321	ACTGGGCGGG TGACCCGCC	GAGGGAATTA CTCCCTTAAT	TTGGCTATTG AACC GATAAC	GCCATTGCAT CGGTAACGTA	ACGTTGTATC TGCAACATAG	TATATCATAA ATATAGTATT	TATGTACATT ATACATGTAA	TATATTGGCT ATATAACCGA
401	CATGTCCAAT GTACAGGTTA	ATGACCGCCA TACTGGCGGT	TGTTGACATT ACAACGTAA	GATTATTGAC CTAATAACTG	TAGTTATTAA ATCAATAATT	TAGTAATCAA ATCATTAGTT	TTACGGGGTC AATGCCCCAG	ATTAGTTCAT TAATCAAGTA
481	AGCCCATATA TCGGGTATAT	TGGAGTTCGG ACCTCAAGGC	CGTTACATAA GCAATGTATT	CTTACGGTAA GAATGCCATT	ATGGCCCCGC TACGGGCGCG	TGGCTGACCG ACCGACTGGC	CCCAACGACC GGGTTGCTGG	CCCGCCCAT GGGCGGGTAA
561	GACGTCAATA CTGCAGTTAT	ATGACGTATG TACTGCATAC	TTCCCATAGT AAGGGTATCA	AACGCCAATA TTGCGGTTAT	GGGACTTTCC CCCTGAAAGG	ATTGACGTCA TAACTGCAGT	ATGGGTGGAG TACCCACCTC	TATTTACGGT ATAAATGCCA
641	AAACTGCCCA TTTGACGGGT	CTTGGCAGTA GAACCGTCAT	CATCAAGTGT GTAGTTCACA	ATCATATGCC TAGTATACGG	AAGTCCGCCC TTCAGGCGGG	CCTATTGACG GGATAACTGC	TCAATGACGG AGTTACTGCC	TAAATGGCCC ATTTACGGGG
721	GCCTGGCATT CGGACCGTAA	ATGCCCAGTA TACGGGTCAT	CATGACCTTA GTACTGGAAT	CGGGACTTTC GCCCTGAAAG	CTACTTGGCA GATGAACCGT	GTACATCTAC CATGTAGATG	GTATTAGTCA CATAATCAGT	TCGCTATTAC AGCGATAATG
801	CATGGTGATG GTACCACTAC	CGGTTTTTGG GCCAAAACCG	AGTACACCAA TCATGTGGTT	TGGGCGTGGA ACCCGCACCT	TAGCGGTTTG ATCGCCAAAC	ACTCACGGGG TGAGTGCCCC	ATTTCCAAGT TAAAGGTTCA	CTCCACCCCA GAGGTGGGGT
881	TTGACGTCAA AACTGCAGTT	TGGGAGTTTG ACCCTCAAAC	TTTTGGCACC AAAACCGTGG	AAAATCAACG TTTTAGTTGC	GGACTTTCCA CCTGAAAGGT	AAATGTCGTA TTTACAGCAT	ATAACCCCGC TATTGGGGCG	CCCGTTGACG GGGCAACTGC
961	CAAATGGGCG GTTTACCCGC	GTAGGCGTGT CATCCGCACA	ACGGTGGGAG TGCCACCCTC	GTCTATATAA CAGATATATT	GCAGAGCTCG CGTCTCGAGC	TTTAGTGAAC AAATCACTTG	CGTCAGATCG GCAGTCTAGC	CCTGGAGACG GGACCTCTGC
1041	CCATCCACGC GGTAGGTGCG	TGTTTTGACC ACAAAACCTG	TCCATAGAAG AGGTATCTTC	ACACCGGGAC TGTGGCCCTG	CGATCCAGCC GCTAGGTCGG	TCCGCGGGCG AGGCGCCGGC	GGAACGGTGC CCTTGCCACG	ATTGGAACGC TAACCTTGCG
1121	GGATTCCCGG CCTAAGGGGC	TGCCAAGAGT ACGTTTCTCA	GACGTAAGTA CTGCATTTCAT	CCGCCTATAG GGCGGATATC	ACTCTATAGG TGAGATATCC	CACACCCCTT GTGTGGGGAA	TGGCTCTTAT ACCGAGAATA	GCATGCTATA CGTACGATAT
1201	CTGTTTTTGG GACAAAAACC	CTTGGGGCCT GAACCCCGGA	ATACACCCCC TATGTGGGGG	GCTCCTTATG CGAGGAATAC	CTATAGGTGA GATATCCACT	TGGTATAGCT ACCATATCGA	TAGCCTATAG ATCGGATATC	GTGTGGGTTA CACACCCAAT
1281	TTGACCATT AACTGGTAAT	TTGACCACTC AACTGGTGAG	CCCTATTGGT GGGATAACCA	GACGATACTT CTGCTATGAA	TCCATTACTA AGGTAATGAT	ATCCATAACA TAGGTATTGT	TGGCTCTTTG ACCGAGAAAC	CCACAACAT GGTGTGTATA
1361	CTCTATTGGC GAGATAACCG	TATATGCCAA ATATACGGTT	TACTCTGTCC ATGAGACAGG	TTCAGAGACT AAGTCTCTGA	GACACGGACT CTGTGCCTGA	CTGTATTTTT GACATAAAAA	ACAGGATGGG TGTCCTACCC	GTCCATTTAT CAGGTAATAA

FIGURE 3 - Page 2

1441 TATTTACAAA TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCGAGTTT TTATTAAACA TAGCGTGGGA TCTCCGACAT
ATAAATGTTT AAGTGTATAT GTTGTTCGGG CAGGGGGCAC GGGCGTCAAA AATAATTTGT ATCGCACCTT AGAGGCTGTA

1521 CTCGGGTACG TGTTCCGGAC ATGGGCTCTT CTCCGGTAGC GGCGGAGCTT CCACATCCGA GCCCTGGTCC CATCCGTCCA
GAGCCCATGC ACAAGGCCTG TACCCGAGAA GAGGCCATCG CCGCCTCGAA GGTGTAGGCT CGGGACCAGG GTAGGACAGT

1601 GCGGCTCATG GTCGCTCGGC AGCTCCTTGC TCCTAACAGT GGAGGCCAGA CTTAGGCACA GCACAATGCC CACCACCACC
CGCCGAGTAC CAGCGAGCCG TCGAGGAACG AGGATTGTCA CCTCCGGTCT GAATCCGTGT CGTGTTACGG GTGGTGGTGG

1681 AGTGTGCCGC ACAAGGCCGT GCGGGTAGGG TATGTGTCTG AAAATGAGCT CGGAGATTGG GCTCGCACCT GGACGCAGAT
TCACACGGCG TGTTCCGGCA CCGCCATCCC ATACACAGAC TTTTACTCGA GCCTCTAACC CGAGCGTGGG CCTGCGTCTA

1761 GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT GAGTTGTGTG ATTCTGATAA GAGTCAGAGG TAACTCCCGT
CCTTCTGAAT TCCGTCGCCG TCTTCTTCTA CGTCCGTCGA CTCAACAACA TAAGACTATT CTCAGTCTCC ATTGAGGGCA

1841 TGCGGTGCTG TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG CGCCACCAGA CATAATAGCT
ACGCCACGAC AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGCGCGCG GCGGTGGTCT GTATTATCGA

+2 M A A
EcoRI
~~~~~

1921 GACAGACTAA CAGACTGTTC CTTTCCATGG GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCTGCAT  
CTGTCTGATT GTCTGACAAG GAAAGGTACC CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGACGTA

---

+2 Y A A Q G Y K V L V L N P S V A A T L G F G A Y M S K  
2001 ATGCAGCTCA GGGCTATAAG GTGCTAGTAC TCAACCCCTC TGTTGCTGCA AACTGGGCT TTGGTGCTTA CATGTCCAAG  
TACGTCGAGT CCCGATATTC CACGATCATG AGTTGGGGAG ACAACGACGT TGTGACCCGA AACCACGAAT GTACAGGTTC

---

+2 A H G I D P N I R T G V R T I T T G S P I T Y S T Y G  
2081 GCTCATGGGA TCGATCCTAA CATCAGGACC GGGGTGAGAA CAATTACCAC TGGCAGCCCC ATCAGCTACT CCACCTACGG  
CGAGTACCTT AGCTAGGATT GTAGTCTCTG CCCCCTCTT GTTAATGGTG ACCGTCGGGG TAGTGCATGA GGTGGATGCC

---

+2 K F L A D G G C S G G A Y D I I I C D E C H S T D A  
2161 CAAGTTCCTT GCCGACGGCG GGTGCTCGGG GGGCGCTTAT GACATAATAA TTTGTGACGA GTGCCACTCC ACGGATGCCA  
GTTCAAGGAA CGGCTGCCGC CCACGAGCCC CCCGGAATA CTGTATTATT AAACACTGCT CACGGTGAGG TGCCTACGGT

---

+2 T S I L G I G T V L D Q A E T A G A R L V V L A T A T  
2241 CATCCATCTT GGGCATTGGC ACTGTCCTTG ACCAAGCAGA GACTGCGGGG GCGAGACTGG TTGTGCTCGC CACCGCCACC  
GTAGGTAGAA CCCGTAACCG TGACAGGAAC TGGTTCGTCT CTGACGCCCC CGCTCTGACC AACACGAGCG GTGGCGGTGG

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+2 P P G S V T V P H P N I E E V A L S T T G E I P F Y G  
2321 CCTCCGGGCT CCGTCACTGT GCGCCATCCC AACATCGAGG AGGTGTCTCT GTCCACCACC GGAGAGATCC CTTTTTACGG  
GGAGGCCCGA GGCAGTGACA CGGGGTAGGG TTGTAGCTCC TCCAACGAGA CAGGTGGTGG CCTCTCTAGG GAAAAATGCC

---

+2 K A I P L E V I K G G R H L I F C H S K K K C D E L  
2401 CAAGGCTATC CCCCTCGAAG TAATCAAGGG GGGGAGACAT CTCATCTTCT GTCATTCAAA GAAGAAGTGC GACGAAGTGC  
GTTCCGATAG GGGGAGCTTC ATTAGTTCCC CCCCTCTGTA GAGTAGAAGA CAGTAAGTTT CTTCTTCACG CTGCTTGAGC

---

+2 A A K L V A L G I N A V A Y Y R G L D V S V I P T S G  
2481 CCGCAAAGCT GGTGCGATTG GGCATCAATG CCGTGGCCTA CTACCGCGGT CTTGACGTGT CCGTCATCCC GACCAGCGGC  
GGCGTTTCGA CCAGCGTAAC CCGTAGTTAC GGCACCGGAT GATGGCGCCA GAAGTGACAG GGCAGTAGGG CTGGTGGCGG

---

+2 D V V V V A T D A L M T G Y T G D F D S V I D C N T C  
2561 GATGTTGTCTG TCGTGGAAC CGATGCCCTC ATGACCGGCT ATACCGGCGA CTTGACTCG GTGATAGACT GCAATACGTG  
CTACAACAGC AGCACCGTTG GCTACGGGAG TACTGGCCGA TATGGCCGCT GAAGCTGAGC CACTATCTGA CGTTATGCAC

DDBJ/EMBL/GenBank

**FIGURE 3 - Page 3**

|      |    |            |            |            |            |             |             |            |            |      |
|------|----|------------|------------|------------|------------|-------------|-------------|------------|------------|------|
|      | +2 | V T Q      | T V D F    | S L D      | P T F      | T I E T     | I T L       | P Q D      | A V S      |      |
| 2641 |    | TGTCACCCAG | ACAGTCGATT | TCAGCCTTGA | CCCTACCTTC | ACCATTGAGA  | CAATCACGCT  | CCCCCAAGAT | GCTGTCTCCC |      |
|      |    | ACAGTGGGTC | TGTCAGCTAA | AGTCGGAAC  | GGGATGGAAG | TGGTAACTCT  | GTTAGTGCGA  | GGGGGTTCTA | CGACAGAGGG |      |
|      | +2 | R T Q R    | R G R      | T G R G    | K P G      | I Y R       | F V A P     | G E R      | P S G      |      |
| 2721 |    | GCACTCAACG | TCGGGGCAGG | ACTGGCAGGG | GGAAGCCAGG | CATCTACAGA  | TTTGTGGCAC  | CGGGGGAGCG | CCCCTCCGGC |      |
|      |    | CGTGAGTTGC | AGCCCCGTCC | TGACCGTCCC | CCTTCGGTCC | GTAGATGTCT  | AAACACCGTG  | GCCCCCTCGC | GGGGAGGCCG |      |
|      | +2 | M F D S    | S V L      | C E C      | Y D A G    | C A W       | Y E L       | T P A E    | T T V      |      |
| 2801 |    | ATGTTGCACT | CGTCCGTCCT | CTGTGAGTGC | TATGACGCAG | GCTGTGCTTG  | GTATGAGCTC  | ACGCCCCCGG | AGACTACAGT |      |
|      |    | TACAAGCTGA | GCAGGCAGGA | GACACTCACG | ATACTGCGTC | CGACACGAAC  | CATACTCGAG  | TGCGGGCGGC | TCTGATGTCA |      |
|      | +2 | R L R      | A Y M N    | T P G      | L P V      | C Q D H     | L E F       | W E G      | V F T      | StuI |
| 2881 |    | TAGGCTACGA | GCGTACATGA | ACACCCCGGG | GCTTCCCCTG | TGCCAGGACC  | ATCTTGAATT  | TTGGGAGGGC | GTCTTTACAG |      |
|      |    | ATCCGATGCT | CGCATGTACT | TGTGGGGGCC | CGAAGGGCAC | ACGGTCCTGG  | TAGAACTTAA  | AACCCTCCCG | CAGAAATGTC |      |
|      | +2 | G L T H    | I D A      | H F L S    | Q T K      | Q S G       | E N L P     | Y L V      | A Y Q      | StuI |
| 2961 |    | GCCTCACTCA | TATAGATGCC | CACTTTCTAT | CCCAGACAAA | GCAGAGTGGG  | GAGAACCCTC  | CTTACCTGGT | AGCGTACCAA |      |
|      |    | CGGAGTGAGT | ATATCTACGG | GTGAAAGATA | GGGTCTGTTT | CGTCTCACCC  | CTCTTGGAAG  | GAATGGACCA | TCGCATGGTT |      |
|      | +2 | A T V C    | A R A      | Q A P      | P P S W    | D Q M       | W K C       | L I R L    | K P T      |      |
| 3041 |    | GCCACCGTGT | GCGCTAGGGC | TCAAGCCCCT | CCCCCATCGT | GGGACCAGAT  | GTGGAAGTGT  | TTGATTCGCC | TCAAGCCCAC |      |
|      |    | CGGTGGCACA | CGCGATCCCG | AGTTCGGGGA | GGGGGTAGCA | CCCTGGTCTA  | CACCTTCACA  | AACTAAGCGG | AGTTCGGGGT |      |
|      | +2 | L H G      | P T P L    | L Y R      | L G A      | V Q N E     | I T L       | T H P      | V T K      |      |
| 3121 |    | CCTCCATGGG | CCAACACCCC | TGCTATACAG | ACTGGGCGCT | GTTCAGAAATG | AAATCACCCCT | GACGCACCCA | GTCAACCAAT |      |
|      |    | GGAGGTACCC | GGTTGTGGGG | ACGATATGTC | TGACCCGCGA | CAAGTCTTAC  | TTTAGTGGGA  | CTGCGTGGGT | CAGTGGTTTA |      |
|      | +2 | Y I M T    | C M S      | A D L E    | V V T      | S T W       | V L V G     | G V L      | A A L      |      |
| 3201 |    | ACATCATGAC | ATGCATGTCT | GCCGACCTGG | AGGTGCTCAC | GAGCACCTGG  | GTGCTCGTTG  | GCGGCGTCCT | GGCTGCTTTG |      |
|      |    | TGTAGTACTG | TACGTACAGC | CGGCTGGACC | TCCAGCAGTG | CTCGTGGACC  | CACGAGCAAC  | CGCCGAGGA  | CCGACGAAAC |      |
|      | +2 | A A Y C    | L S T      | G C V      | V I V G    | R V V       | L S G       | K P A I    | I P D      |      |
| 3281 |    | GCCGCGTATT | GCCTGTCAAC | AGGCTGCGTG | GTCATAGTGG | GCAGGGTCGT  | CTTGTCCGGG  | AAGCCGGCAA | TCATACCTGA |      |
|      |    | CGGCGCATAA | CGGACAGTTG | TCCGACGCAC | CAGTATCACC | CGTCCCAGCA  | GAACAGGCCC  | TTCGGCCGTT | AGTATGGACT |      |
|      | +2 | R E V      | L Y R E    | F D E      | M E E      | C S Q H     | L P Y       | I E Q      | G M M      |      |
| 3361 |    | CAGGGAAGTC | CTCTACCGAG | AGTTCGATGA | GATGGAAGAG | TGCTCTCAGC  | ACTTACCGTA  | CATCGAGCAA | GGGATGATGC |      |
|      |    | GTCCCTTCAG | GAGATGGCTC | TCAAGCTACT | CTACCTTCTC | ACGAGAGTCG  | TGAATGGCAT  | GTAGCTCGTT | CCCTACTACG |      |
|      | +2 | L A E Q    | F K Q      | K A L G    | L L Q      | T A S       | R Q A E     | V I A      | P A V      |      |
| 3441 |    | TCGCCGAGCA | GTTCAAGCAG | AAGGCCCTCG | GCCTCCTGCA | GACCGCGTCC  | CGTCAGGCAG  | AGGTTATCGC | CCCTGCTGTC |      |
|      |    | AGCGGCTCGT | CAAGTTCGTC | TTCCGGGAGC | CGGAGGACGT | CTGGCGCAGG  | GCAGTCCGTC  | TCCAATAGCG | GGGACGACAG |      |
|      | +2 | Q T N W    | Q K L      | E T F      | W A K H    | M W N       | F I S       | G I Q Y    | L A G      |      |
| 3521 |    | CAGACCAACT | GGCAAAAACT | CGAGACCTTC | TGGGGCAAGC | ATATGTGGAA  | CTTCATCAGT  | GGGATACAAT | ACTTGGCGGG |      |
|      |    | GTCTGGTTGA | CCGTTTTTGA | GCTCTGGAAG | ACCCGCTTCG | TATACACCTT  | GAAGTAGTCA  | CCCTATGTTA | TGAACCGCCC |      |
|      | +2 | L S T      | L P G N    | P A I      | A S L      | M A F T     | A A V       | T S P      | L T T      |      |
| 3601 |    | CTTGTCACAG | CTGCCTGGTA | ACCCCGCCAT | TGCTTCATTG | ATGGCTTTTA  | CAGCTGCTGT  | CACCAGCCCA | CTAACCCTTA |      |
|      |    | GAACAGTTGC | GACGGACCAT | TGGGGCGGTA | ACGAAGTAAC | TACCGAAAAT  | GTCGACGACA  | GTGGTCGGGT | GATTGGTGAT |      |
|      | +2 | S Q T L    | L F N      | I L G G    | W V A      | A Q L       | A A P G     | A A T      | A F V      |      |
| 3681 |    | GCCAAACCCT | CCTCTTCAAC | ATATTGGGGG | GGTGGGTGGC | TGCCAGCTC   | GCCGCCCCCG  | GTGCCGCTAC | TGCCTTTGTG |      |
|      |    | CGGTTTGGGA | GGAGAAGTTG | TATAACCCCC | CCACCCACCG | ACGGGTGCGAG | CGGCGGGGGC  | CACGGCGATG | ACGGAAACAC |      |

## FIGURE 3 - Page 4

+2 G A G L A G A A I G S V G L G K V L I D I L A G Y G A  
 3761 GGGCGTGGCT TAGCTGGCGC CGCCATCGGC AGTGTGGAC TGGGAAGGT CCTCATAGAC ATCCTTGACG GGTATGGCGC  
 CCGCGACCGA ATCGACCGCG GCGGTAGCCG TCACAACTG ACCCCTTCCA GGAGTATCTG TAGGAACGTC CCATACCGCG

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+2 G V A G A L V A F K I M S G E V P S T E D L V N L L  
 3841 GGGCGTGGCG GGAGCTCTTG TGGCATTCAA GATCATGAGC GGTGAGGTCC CCTCCACGGA GGACCTGGTC AATCTACTGC  
 CCCGCACCGC CCTCGAGAAC ACCGTAAGTT CTAGTACTCG CCACTCCAGG GGAGGTGCCT CCTGGACCAG TTAGATGACG

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+2 P A I L S P G A L V V G V V C A A I L R R H V G P G E  
 3921 CCGCCATCCT CTCGCCCGGA GCCCTCGTAG TCGGCGTGGT CTGTGCAGCA ATACTGCGCC GGCACGTTGG CCCGGGCGAG  
 GCGGCTAGGA GAGCGGGCCT CGGGAGCATC AGCCGCACCA GACACGTCGT TATGACGCGG CCGTGCAACC GGGCCCCGCTC

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+2 G A V Q W M N R L I A F A S R G N H V S P T H Y V P E  
 4001 GGGCAGTGC AGTGGATGAA CCGGCTGATA GCCTTCGCCT CCCGGGGGAA CCATGTTTCC CCCACGCACT ACGTGCCGGA  
 CCCCGTCACG TCACCTACTT GGCCGACTAT CGGAAGCGGA GGGCCCCCTT GGTACAAAGG GGGTGCCTGA TGCACGGCCT

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+2 S D A A A R V T A I L S S L T V T Q L L R R L H Q W  
 4081 GAGCGATGCA GGTGCCCCGCG TCACTGCCAT ACTCAGCAGC CTCAGTGTAA CCCAGCTCCT GAGGCGACTG CACCAGTGA  
 CTCGCTACGT CGACGGGCGC AGTGACGGTA TGAGTCGTCG GAGTGACATT GGGTCGAGGA CTCCGCTGAC GTGGTCACCT

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+2 I S S E C T T P C S G S W L R D I W D W I C E V L S D  
 4161 TAAGCTCGGA GTGTACCACT CCATGCTCCG GTTCCTGGCT AAGGGACATC TGGGACTGGA TATGCGAGGT GTTGAGCGAC  
 ATTCGAGCCT CACATGGTGA GGTACGAGGC CAAGGACCGA TTCCCTGTAG ACCCTGACCT ATACGCTCCA CAACTCGCTG

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+2 F K T W L K A K L M P Q L P G I P F V S C Q R G Y K G  
 BamHI  
 ~~~~~  
 4241 TTTAAGACCT GGCTAAAAGC TAAGCTCATG CCACAGCTGC CTGGGATCCC CTTTGTGTCC TGCCAGCGCG GGTATAAGGG
 AAATTCTGGA CCGATTTTCG ATTCGAGTAC GGTGTCGACG GACCCTAGGG GAAACACAGG ACGGTGCGCG CCATATTCCC

+2 V W R G D G I M H T R C H C G A E I T G H V K N G T
 4321 GGTCTGGCGA GGGGACGGCA TCATGCACAC TCGCTGCCAC TGTGGAGCTG AGATCACTGG ACATGTCAAA AACGGGACGA
 CCAGACCGCT CCCCTGCCGT AGTACGTGTG AGCGACGGTG ACACCTCGAC TCTAGTGACC TGTACAGTTT TTGCCCTGCT

+2 M R I V G P R T C R N M W S G T F P I N A Y T T G P C
 4401 TGAGGATCGT CCGTCCTAGG ACCTGCAGGA ACATGTGGAG TGGGACCTTC CCCATTAATG CCTACACCAC GGGCCCCGTGT
 ACTCCTAGCA GCCAGGATCC TGGACGTCCT TGTACACCTC ACCCTGGAAG GGGTAATTAC GGATGTGGTG CCCGGGGACA

+2 T P L P A P N Y T F A L W R V S A E E Y V E I R Q V G
 4481 ACCCCCTTC CTGCGCCGAA CTACACGTTT GCGCTATGGA GGGTGTCTGC AGAGGAATAC GTGGAGATAA GGCAGGTGGG
 TGGGGGGAAG GACGCGGCTT GATGTGCAAG CGCGATACCT CCCACAGACG TCTCCTTATG CACCTCTATT CCGTCCACCC

+2 D F H Y V T G M T T D N L K C P C Q V P S P E F F T
 4561 GGAFTTCCAC TACGTGACGG GTATGACTAC TGACAATCTT AAATGCCCCG GCCAGGTCCC ATCGCCCGAA TTTTTCACAG
 CCTGAAGGTG ATGCACTGCC CATACTGATG ACTGTTAGAA TTTACGGGCA CCGTCCAGGG TAGCGGGCTT AAAAAGTGTG

+2 E L D G V R L H R F A P P C K P L L R E E V S F R V G
 4641 AATTGGACGG GGTGCGCCTA CATAGGTTTG CGCCCCCTG CAAGCCCTTG CTGCGGGAGG AGGTATCATT CAGAGTAGGA
 TTAACCTGCC CCACGCGGAT GTATCCAAAC GCGGGGGGAC GTTCGGGAAC GACGCCCTCC TCCATAGTAA GTCTCATCCT

+2 L H E Y P V G S Q L P C E P E P D V A V L T S M L T D
 4721 CTCCACGAAT ACCCGGTAGG GTCGCAATTA CTTTGCAGC CCGAACCGGA CGTGGCCGTG TTGACGTCCA TGCTCACTGA
 GAGGTGCTTA TGGGCCATCC CAGCGTTAAT GGAACGCTCG GGCTTGGCCT GCACCGGCAC AACTGCAGGT ACGAGTGACT

+2 P S H I T A E A A G R R L A R G S P P S V A S S S A
 4801 TCCCTCCCAT ATAACAGCAG AGGCGGCGCG GCGAAGGTTG GCGAGGGGAT CACCCCTCCT TGTGGCCAGC TCCTCGGCTA
 AGGGAGGGTA TATTGTCGTC TCCGCGGCGC CGCTTCCAAC CGTCCCCTA GTGGGGGGAG ACACCGGTG AGGAGCCGAT

+2	S	Q	L	S	A	P	S	L	K	A	T	C	T	A	N	H	D	S	P	D	A	E	L	I	E	A	N
4881	GCCAGCTATC	CGCTCCATCT	CTCAAGGCAA	CTTGACCGC	TAACCATGAC	TCCCCTGATG	CTGAGCTCAT	AGAGGCCAAC	CGGTCGATAG	GCGAGGTAGA	GAGTTCCGTT	GAACGTGGCG	ATTGTTACTG	AGGGGACTAC	GACTCGAGTA	TCTCCGGTTG											
+2	L	L	W	R	Q	E	M	G	G	N	I	T	R	V	E	S	E	N	K	V	V	I	L	D	S	F	D
4961	CTCCTATGGA	GGCAGGAGAT	GGGCGGCAAC	ATCACCAGGG	TTGAGTCAGA	AAACAAAGTG	GTGATTCTGG	ACTCCTTCGA	GAGGATACCT	CCGTCTCTA	CCCGCCGTTG	TAGTGGTCCC	AACTCAGTCT	TTTGTTCAC	CACCTAAGACC	TGAGGAAGCT											
+2	P	L	V	A	E	E	D	E	R	E	I	S	V	P	A	E	I	L	R	K	S	R	R	F	A	Q	
5041	TCCGCTTGTT	GCGGAGGAGG	ACGAGCGGGA	GATCTCCGTA	CCCGCAGAAA	TCTTGCAGAA	GTCTCGGAGA	TTCGCCCAGG	AGGCGAACAC	CGCTCTCTCC	TGCTCGCCCT	CTAGAGGCAT	GGGCGTCTTT	AGGACGCCTT	CAGAGCCTCT	AAGCGGGTCC											
+2	A	L	P	V	W	A	R	P	D	Y	N	P	P	L	V	E	T	W	K	K	P	D	Y	E	P	P	V
5121	CCCTGCCCCG	TTGGGCGCGG	CCGGACTATA	ACCCCCCGCT	AGTGGAGACG	TGGAAGAAAG	CCGACTACGA	ACCACCTGTG	GGGACGGGCA	AACCCGCGCC	GGCTGATAT	TGGGGGGCGA	TCACCTCTGC	ACCTTTTTTC	GGCTGATGCT	TGGTGGACAC											
+2	V	H	G	C	P	L	P	P	P	K	S	P	P	V	P	P	P	R	K	K	R	T	V	V	L	T	E
5201	GTCCATGGCT	GCCCGCTTCC	ACCTCCAAAG	TCCCCTCTCG	TGCCTCCGCC	TCGGAAGAAG	CGGACGGTGG	TCCTCACTGA	CAGGTACCGA	CGGGCGAAGG	TGGAGGTTTC	AGGGGAGGAC	ACGGAGGCGG	AGCCTTCTTC	GCCTGCCACC	AGGAGTGACT											
+2	S	T	L	S	T	A	L	A	E	L	A	T	R	S	F	G	S	S	S	T	S	G	I	T	G	D	
5281	ATCAACCCTA	TCTACTGCCT	TGGCCGAGCT	CGCCACCAGA	AGCTTTGGCA	GCTCCTCAAC	TTCCGGCATT	ACGGGCGACA	TAGTTGGGAT	AGATGACGGA	ACCGGCTCGA	GCGGTGGTCT	TCGAAACCGT	CGAGGAGTTG	AAGGCCGTAA	TGCCCGCTGT											
+2	N	T	T	T	S	S	E	P	A	P	S	G	C	P	P	D	S	D	A	E	S	Y	S	S	M	P	P
5361	ATACGACAAC	ATCCTCTGAG	CCCGCCCCCT	CTGGCTGCCC	CCCCGACTCC	GACGCTGAGT	CCTATTCTCT	CATGCCCCCC	TATGCTGTTG	TAGGAGACTC	GGGCGGGGAA	GACCGACGGG	GGGGCTGAGG	CTGCGACTCA	GGATAAGGAG	GTACGGGGGG											
+2	L	E	G	E	P	G	D	P	D	L	S	D	G	S	W	S	T	V	S	S	E	A	N	A	E	D	V
							BamHI																				
5441	CTGGAGGGGG	AGCCTGGGGA	TCCGGATCTT	AGCGACGGGT	CATGGTCAAC	GGTCAGTAGT	GAGGCCAACG	CGGAGGATGT	GACCTCCCCC	TCGGACCCCT	AGGCCTAGAA	TCGCTGCCCA	GTACCAGTTG	CCAGTCATCA	CTCCGGTTGC	GCCTCTTACA											
+2	V	C	C	S	M	S	Y	S	W	T	G	A	L	V	T	P	C	A	A	E	E	Q	K	L	P	I	
5521	CGTGTGCTGC	TCAATGTCTT	ACTCTTGAGC	AGGCGCACTC	GTCACCCCGT	GCGCGCGGGA	AGAACAGAAA	CTGCCCATCA	GCACACGACG	AGTTACAGAA	TGAGAACCTG	TCCGCGTGAG	CAGTGGGGCA	CGCGGCGCCT	TCTTGTCTTT	GACGGGTAGT											
+2	N	A	L	S	N	S	L	L	R	H	H	N	L	V	Y	S	T	T	S	R	S	A	C	Q	R	Q	K
5601	ATGCACTAAG	CAACTCGTTG	CTACGTCACC	ACAATTTGGT	GTATTCCACC	ACCTCACGCA	GTGCTTGCCA	AAGGCAGAAG	TACGTGATTC	GTTGAGCAAC	GATGCAGTGG	TGTTAAACCA	CATAAGGTGG	TGGAGTGCCT	CACGAACGGT	TTCCGTCTTC											
+2	K	V	T	F	D	R	L	Q	V	L	D	S	H	Y	Q	D	V	L	K	E	V	K	A	A	A	S	K
5681	AAAGTCACAT	TTGACAGACT	GCAAGTTCTG	GACAGCCATT	ACCAGGACGT	ACTCAAGGAG	GTAAAGCAG	CGGCGTCAAA	TTTCAGTGTA	AACTGTCTGA	CGTTCAAGAC	CTGTCGGTAA	TGGTCTCTGA	TGAGTTCTCT	CAATTTCTGC	GCCGCAAGTT											

FIGURE 3 - Page 6

	R	L	I	V	F	P	D	L	G	V	R	V	C	E	K	M	A	L	Y	D	V	V	T	K	L	P	
6001	TCGTCTCATC	GTGTTCCCCG	ATCTGGGCGT	GCGCGTGTGC	GAAAAGATGG	CTTTGTACGA	CGTGGTTACA	AAGCTCCCCT	AGCAGAGTAG	CACAAGGGGC	TAGACCCGCA	CGCGCACACG	CTTTTCTACC	GAAACATGCT	GCACCAATGT	TTCGAGGGGA											
+2	L	A	V	M	G	S	S	Y	G	F	Q	Y	S	P	G	Q	R	V	E	F	L	V	Q	A	W	K	S
																			EcoRI								
6081	TGGCCGTGAT	GGGAAGCTCC	TACGGATTCC	AATACTCACC	AGGACAGCGG	GTTGAATTCC	TCGTGCAAGC	GTGGAAGTCC	ACCGGCACTA	CCCTTCGAGG	ATGCCTAAGG	TTATGAGTGG	TCCTGTGCGC	CAACTTAAGG	AGCACGTTTC	CACCTTCAGG											
+2	K	K	T	P	M	G	F	S	Y	D	T	R	C	F	D	S	T	V	T	E	S	D	I	R	T	E	E
6161	AAGAAAACCC	CAATGGGGTT	CTCGTATGAT	ACCGCTGTCT	TTGACTCCAC	AGTCACTGAG	AGCGACATCC	GTACGGAGGA	TTCTTTTGGG	GTTACCCCAA	GAGCATACTA	TGGGCGACGA	AACTGAGGTG	TCAGTGACTC	TCGCTGTAGG	CATGCCTCCT											
+2	A	I	Y	Q	C	C	D	L	D	P	Q	A	R	V	A	I	K	S	L	T	E	R	L	Y	V	G	
6241	GGCAATCTAC	CAATGTTGTG	ACCTCGACCC	CCAAGCCCGC	GTGGCCATCA	AGTCCCTCAC	CGAGAGGCTT	TATGTTGGGG	CCGTTAGATG	GTTACAACAC	TGGAGCTGGG	GGTTCGGGCG	CACCGGTAGT	TCAGGGAGTG	GCTCTCCGAA	ATACAACCCC											
+2	G	P	L	T	N	S	R	G	E	N	C	G	Y	R	R	C	R	A	S	G	V	L	T	T	S	C	G
6321	GCCCTCTTAC	CAATTCAAGG	GGGGAGAACT	GCGGCTATCG	CAGGTGCCGC	GCGAGCGGCG	TACTGACAAC	TAGCTGTGGT	CGGGAGAAATG	GTTAAGTTC	CCCCTCTTGA	CGCCGATAGC	GTCCACGGCG	CGCTCGCCGC	ATGACTGTTG	ATCGACACCA											
+2	N	T	L	T	C	Y	I	K	A	R	A	A	C	R	A	A	G	L	Q	D	C	T	M	L	V	C	G
6401	AACACCCTCA	CTTGCTACAT	CAAGGCCCGG	GCAGCCTGTC	GAGCCGCAGG	GCTCCAGGAC	TGCACCATGC	TCGTGTGTGG	TTGTGGGAGT	GAACGATGTA	GTTCCGGGCC	CGTCGGACAG	CTCGGCGTCC	CGAGGTCTCTG	ACGTGGTACG	AGCACACACC											
+2	D	D	L	V	V	I	C	E	S	A	G	V	Q	E	D	A	A	S	L	R	A	F	T	E	A	M	
6481	CGACGACTTA	GTCGTTATCT	GTGAAAGCGC	GGGGGTCCAG	GAGGACGCGG	CGAGCCTGAG	AGCCTTCACG	GAGGCTATGA	GCTGCTGAAT	CAGCAATAGA	CACTTTCGCG	CCCCCAGGTC	CTCCTGCGCC	GCTCGGACTC	TCGGAAGTGC	CTCCGATACT											
+2	T	R	Y	S	A	P	P	G	D	P	P	Q	P	E	Y	D	L	E	L	I	T	S	C	S	S	N	V
6561	CCAGGTACTC	CGCCCCCCT	GGGGACCCCC	CACAACCAGA	ATACGACTTG	GAGCTCATAA	CATCATGCTC	CTCCAACGTG	GGTCCATGAG	GCGGGGGGGA	CCCCTGGGGG	GTGTTGGTCT	TATGCTGAAC	CTCGAGTATT	GTAGTACGAG	GAGGTTGCAC											
+2	S	V	A	H	D	G	A	G	K	R	V	Y	Y	L	T	R	D	P	T	T	P	L	A	R	A	A	W
6641	TCAGTCGCCC	ACGACGGCGC	TGGAAGAGAG	GTCTACTACC	TCACCCGTGA	CCCTACAACC	CCCCTCGCGA	GAGCTGCGTG	AGTCAGCGGG	TGCTGCCGCG	ACCTTTCTCC	CAGATGATGG	AGTGGGCACT	GGGATGTTGG	GGGGAGCGCT	CTCGACGCAC											
+2	E	T	A	R	H	T	P	V	N	S	W	L	G	N	I	I	M	F	A	P	T	L	W	A	R	M	
6721	GGAGACAGCA	AGACACACTC	CAGTCAATTC	CTGGCTAGGC	AACATAATCA	TGTTTGCCCC	CACACTGTGG	GCGAGGATGA	CCTCTGTCGT	TCTGTGTGAG	GTCAGTTAAG	GACCGATCCG	TTGTATTAGT	ACAAACGGGG	GTGTGACACC	CGCTCTACT											
+2	I	L	M	T	H	F	F	S	V	L	I	A	R	D	Q	L	E	Q	A	L	D	C	E	I	Y	G	A
6801	TACTGATGAC	CCATTTCTTT	AGCGTCCTTA	TAGCCAGGGA	CCAGCTTGAA	CAGGCCCTCG	ATTGCGAGAT	CTACGGGGCC	ATGACTACTG	GGTAAAGAAA	TCGCAGGAAT	ATCGGTCCCT	GGTCAACTT	GTCCGGGAGC	TAACGCTCTA	GATGCCCGGG			</								

FIGURE 3 - Page 7

+2 R T K L K L T P I A A A G Q L D L S G W F T A G Y S G
 7121 AGAACAAAGC TCAAACAC TCCAATAGCG GCCGCTGGCC AGCTGGACTT GTCCGGCTGG TTCACGGCTG GCTACAGCGG
 TCTTGTTCG AGTTTGAGTG AGGTTATCGC CGGCGACCGG TCGACCTGAA CAGGCCGACC AAGTGCCGAC CGATGTCGCC

+2 G D I Y H S V S H A R P R W I W F C L L L L A A G V
 7201 GGGAGACATT TATCACGCG TGTCTCATGC CCGGCCCGC TGGATCTGGT TTTGCCTACT CCTGCTTGCT GCAGGGGTAG
 CCCTCTGTAA ATAGTGTGCG ACAGAGTACG GGCCGGGGCG ACCTAGACCA AAACGGATGA GGACGAACGA CGTCCCCATC

+2 G I Y L L P N R
 7281 GCATCTACCT CCTCCCCAAC CGATGAAGGT TGGGGTAAAC ACTCCGGCCT AAAAAAAAAA AAAAATCTAG AAAGGCGCGC
 CGTAGATGGA GGAGGGGTTG GCTACTTCCA ACCCCATTG TGAGGCCGGA TTTTTTTTTT TTTTATAGTC TTTCCGCGCG

. BamHI MluI
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 7361 CAAGATATCA AGGATCCACT ACGCGTTAGA GCTCGCTGAT CAGCCTCGAC TGTGCCTTCT AGTTGCCAGC CATCTGTTGT  
 GTTCTATAGT TCCTAGGTGA TCGCAATCT CGAGCGACTA GTCGGAGCTG ACACGGAAGA TCAACGGTCG GTAGACAACA

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7441 TTGCCCCCTCC CCCGTGCCTT CTTGACCCT GGAAGGTGCC ACTCCACTG TCCTTTCCTA ATAAATGAG GAAATTGCAT  
 AACGGGGAGG GGGCACGGAA GGAAGTGGGA CTTCCACGG TGAGGGTGAC AGGAAAGGAT TATTTTACTC CTTTAACTGA

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7521 CGCATTGTCT GAGTAGGTGT CATTCTATTC TGGGGGGTGG GGTGGGGCAG GACAGCAAGG GGGAGGATTG GGAAGACAAT  
 GCGTAACAGA CTCATCCACA GTAAGATAAG ACCCCCCACC CCACCCCGTC CTGTCGTTCC CCCTCCTAAC CCTTCTGTTA

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7601 AGCAGGCATG CTGGGGAGCT CTTCCGCTTC CTCGCTCACT GACTCGCTGC GCTCGGTCGT TCGGCTGCGG CGAGCGGTAT  
 TCGTCCGTAC GACCCCTCGA GAAGGCGAAG GAGCGAGTGA CTGAGCGACG CGAGCCAGCA AGCCGACGCC GCTCGCCATA

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7681 CAGCTCACTC AAAGGCGGTA ATACGGTTAT CCACAGAATC AGGGGATAAC GCAGGAAAGA ACATGTGAGC AAAAGGCCAG  
 GTCGAGTGAG TTTCCGCCAT TATGCCAATA GGTGTCTTAG TCCCTATTG CGTCTTTTCT TGTACACTCG TTTTCCGGTC

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7761 CAAAAGGCCA GGAACCGTAA AAAGGCCGCG TTGCTGGCGT TTTTCCATAG GCTCCGCCCC CCTGACGAGC ATCACAACAA  
 GTTTTCCGGT CCTTGGCATT TTTCCGGCGC AACGACCGCA AAAAGGTATC CGAGGCCGGG GGACTGCTCG TAGTGTTTT

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7841 TCGACGCTCA AGTCAGAGGT GGCGAAACCC GACAGGACTA TAAAGATACC AGGCGTTTCC CCCTGGAAGC TCCCTCGTGC  
 AGCTGCGAGT TCAGTCTCCA CCGCTTTGGG CTGTCTGAT ATTTCTATGG TCCGCAAAGG GGGACCTTCG AGGGAGCAGC

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7921 GCTCTCTGT TCCGACCCTG CCGCTTACCG GATACCTGTC CGCCTTTCTC CCTTCGGGAA GCGTGGCGCT TTCTCAATGC  
 CGAGAGGACA AGGCTGGGAC GGCGAATGGC CTATGGACAG GCGGAAAGAG GGAAGCCCTT CGCACCAGCA AAGAGTTACG

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8001 TCACGCTGTA GGTATCTCAG TTCGGTGTAG GTCGTTTCGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG TTCAGCCCCA  
 AGTGCGACAT CCATAGAGTC AAGCCACATC CAGCAAGCGA GGTTCGACCC GACACACGTG CTTGGGGGGC AAGTCGGGCT

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8081 CCGCTGCGCC TTATCCGGTA ACTATCGTCT TGAGTCCAAC CCGGTAAGAC ACGACTTATC GCCACTGGCA GCAGCCACTG  
 GGCGACGCGG AATAGGCCAT TGATAGCAGA ACTCAGGTTG GGCCATTCTG TGCTGAATAG CCGTGACCGT CGTCGGTGAC

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8161 GTAACAGGAT TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC CTAACACGG CTACACTAGA  
 CATTGTCCTA ATCGTCTCGC TCCATACATC CGCCACGATG TCTCAAGAAC TTCACCACCG GATTGATGCC GATGTGATCT

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8241 AGGACAGTAT TTGGTATCTG CGCTCTGCTG AAGCCAGTTA CTTTCGGAAA AAGAGTTGGT AGCTCTTGAT CCGGCAACAA  
 TCCTGTCATA AACCATAGAC GCGAGACGAC TTCGGTCAAT GGAAGCCCTT TTCTCAACCA TCGAGAACTA GGCCGTTTGT

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8321 AACCACCGCT GGTAGCGGTG GTTTTTTGT TTGCAAGCAG CAGATTACGC GCAGAAAAAA AGGATCTCAA GAAGATCCTT  
 TTGGTGGCGA CCATCGCCAC CAAAAAACA AACGTTTCGTC GTCTAATGCG CGTCTTTTTT TCCTAGAGTT CTTCTAGGAA

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8401 TGATCTTTTC TACGGGGTCT GACGCTCAGT GGAACGAAAA CTCACGTAA GGGATTTTGG TCATGAGATT ATCAAAAAGG  
 ACTAGAAAAG ATGCCCCAGA CTGCGAGTCA CCTTGCTTTT GAGTGCAATT CCCTAAAACC AGTACTCTAA TAGTTTTTCC

## FIGURE 3 - Page 8

8481 ATCTTCACCT AGATCCTTTT AAATTAAAAA TGAAGTTTTA AATCAATCTA AAGTATATAT GAGTAAACTT GGTCTGACAG  
TAGAAGTGGA TCTAGGAAAA TTTAATTTTT ACTTCAAAAT TTAGTTAGAT TTCATATATA CTCATTTGAA CCAGACTGTC

---

8561 TTACCAATGC TTAATCAGTG AGGCACCTAT CTCAGCGATC TGTCTATTTC GTTCATCCAT AGTTGCCTGA CTCCTCGTCG  
AATGGTTACG AATTAGTCAC TCCGTGGATA GAGTCGCTAG ACAGATAAAG CAAGTAGGTA TCAACGGACT GAGGGGCAGC

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8641 TGTAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA ATGATACCGC GAGACCCACG CTCACCGGCT  
ACATCTATTG ATGCTATGCC CTCCGAATG GTAGACCGGG GTCACGACGT TACTATGGCG CTCTGGGTGC GAGTGGCCGA

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8721 CCAGATTTAT CAGCAATAAA CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG CCTCCATCCA  
GGTCTAAATA GTCGTTATTT GGTCGGTCCG CCTTCCCGGC TCGCGTCTTC ACCAGGACGT TGAAATAGGC GGAGGTAGGT

---

8801 GTCTATTAAT TGTGCGGGG AAGCTAGAGT AAGTAGTTCG CCAGTTAATA GTTTGCGCAA CGTTGTTGCC ATTGCTACAG  
CAGATAATTA ACAACGGCCC TTCGATCTCA TTCATCAAGC GGTCAATTAT CAAACGCGTT GCAACAACGG TAACGATGTC

---

8881 GCATCGTGGT GTCACGCTCG TCGTTTGGA TGGCTTCATT CAGCTCCGGT TCCCAACGAT CAAGGCGAGT TACATGATCC  
CGTAGCACCA CAGTGCGAGC AGCAAACCAT ACCGAAGTAA GTCGAGGCCA AGGGTTGCTA GTTCCGCTCA ATGTACTAGG

---

8961 CCCATGTTGT GCAAAAAAGC GGTTAGCTCC TTCGGTCCTC CGATCGTTGT CAGAAGTAAG TTGGCCGCAG TGTATCACT  
GGGTACAACA CGTTTTTTCG CCAATCGAGG AAGCCAGGAG GCTAGCAACA GTCTTCATTC AACC GGCGTC ACAATAGTGA

---

9041 CATGGTTATG GCAGCACTGC ATAATTCTCT TACTGTCATG CCATCCGTAA GATGCTTTTC TGTGACTGGT GAGTACTCAA  
GTACCAATAC CGTCGTGACG TATTAAGAGA ATGACAGTAC GGTAGGCATT CTACGAAAAG AACTGACCA CTCATGAGTT

---

9121 CCAAGTCATT CTGAGAATAG TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAATAC GGGATAATAC CGCGCCACAT  
GGTTCAGTAA GACTCTTATC ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTATG CCCTATTATG GCGCGGTGTA

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9201 AGCAGAACTT TAAAGTGCT CATCATTGGA AAACGTTCTT CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC  
TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA GCCCGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG

---

9281 CAGTTCGATG TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG CGTTTCTGGG TGAGCAAAAA  
GTCAAGCTAC ATTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGGTC GCAAAGACCC ACTCGTTTTT

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9361 CAGGAAGGCA AAATGCCGCA AAAAAGGGAA TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCCT TTTTCAATAT  
GTCCTTCCGT TTTACGGCGT TTTTCCCTT ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

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9441 TATTGAAGCA TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTTGA ATGTATTTAG AAAAATAAAC AAATAGGGGT  
ATAACTTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT TACATAAATC TTTTATTG TTTATCCCA

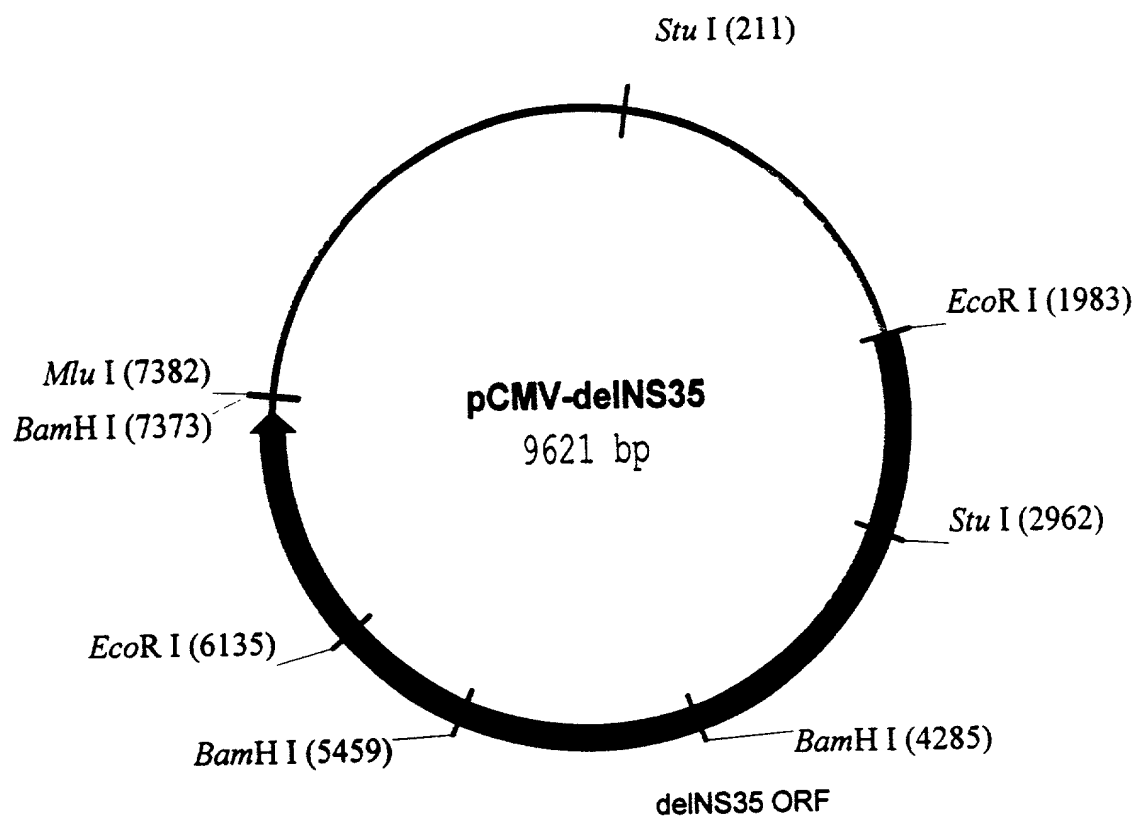
---

9521 TCCGCGCACA TTTCCCCGAA AAGTGCCACC TGACGTCTAA GAAACCATTA TTATCATGAC ATTAACCTAT AAAAATAGGC  
AGGCGCGTGT AAAGGGGCTT TTCACGGTGG ACTGCAGATT CTTTGGTAAT AATAGTACTG TAATTGGATA TTTTATCCG

---

9601 GTATCAGAG GCCCTTTCGT C  
CATAGTGCTC CGGAAAGCA G

FIGURE 4



## FIGURE 5 - Page 1

1 TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG GAGACGGTCA CAGCTTGTCT GTAAGCGGAT  
AGCGCGCAAA GCCACTACTG CCACCTTTTG AGACTGTGTA CGTCGAGGGC CTCTGCCAGT GTCGAACAGA CATTGCGCTA

---

81 GCCGGGAGCA GACAAGCCCG TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG CGGCATCAGA  
CGGCCCTCGT CTGTTCCGGC AGTCCCGCGC AGTCGCCCAC AACCGCCCAC AGCCCCGACC GAATTGATAC GCCGTAGTCT

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161 GCAGATTGTA CTGAGAGTGC ACCATATGAA GCTTTTGTGA AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG
CGTCTAACAT GACTCTCAGC TGGTATACTT CGAAAAACGT TTTCGGATCC GGAGGTTTTT TCGGAGGAGT GATGAAGACC

241 AATAGCTCAG AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAT TAGTCAGCCA TGGGGCGGAG AATGGGCGGA
TTATCGAGTC TCCGGTCCG CCGGAGCCGG AGACGTATTT ATTTTTTTTA ATCAGTCGGT ACCCGCGCTC TTACCCGCTC

321 ACTGGGCGGG GAGGGAATTA TTGGCTATTG GCCATTGCAT ACGTTGTATC TATATCATAA TATGTACATT TATATTGGCT
TGACCCGCCC CTCCCTTAAT AACCGATAAC CGGTAACGTA TGCAACATAG ATATAGTATT ATACATGTAA ATATAACCGA

401 CATGTCCAAT ATGACCGCCA TGTTGACATT GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT
GTACAGGTTA TACTGGCGGT ACAACTGTAA CTAATAACTG ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA

481 AGCCCATATA TGGAGTTCGG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC CCCGCCATT
TCGGGTATAT ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC GGGTTGCTGG GGGCGGGTAA

561 GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTACGGT
CTGCAGTTAT TACTGCATAC AAGGGTATCA TTGCGGTTAT CCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

641 AAAGTGGCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTCCGCCC CCTATTGACG TCAATGACGG TAAATGGCCC
TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCAGGCGGG GGATAACTGC AGTTACTGCC ATTTACCGGG

721 GCCTGGCATT ATGCCCAGTA CATGACCTTA CGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA TCGCTATTAC
CGGACCGTAA TACGGGTCAT GTACTGGAAT GCCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT AGCGATAATG

801 CATGGTGATG CGGTTTTGGC AGTACACCAA TGGGCGTGA TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA
GTACCACTAC GCCAAAACCG TCATGTGGTT ACCCGCACCT ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT

881 TTGACGTCAA TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA ATAACCCCGC CCCGTTGACG
AACTGCAGTT ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT TATTGGGGCG GGGCAACTGC

961 CAAATGGGCG GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
GTTTACCCGC CATCCGCACA TGCCACCTC CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1041 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC TCCGCGGCCG GGAACGGTGC ATTGGAACGC
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG AGGCGCCGGC CCTTGCCACG TAACCTTGCG

1121 GGATTCCCCG TGCCAAGAGT GACGTAAGTA CCGCCTATAG ACTCTATAGG CACACCCCTT TGGCTCTTAT GCATGCTATA
CCTAAGGGGC ACGGTTCTCA CTGCATTCAT GGCGGATATC TGAGATATCC GTGTGGGGAA ACCGAGAATA CGTACGATAT

1201 CTGTTTTTGG CTTGGGGCCT ATACACCCCC GCTCCTTATG CTATAGGTGA TGGTATAGCT TAGCCTATAG GTGTGGGTTA
GACAAAAACC GAACCCCGGA TATGTGGGGG CGAGGAATAC GATATCCACT ACCATATCGA ATCGGATATC CACACCCAAT

1281 TTGACCATTA TTGACCACTC CCCTATTGGT GACGATACTT TCCATTACTA ATCCATAACA TGGCTCTTTG CCACAACAT
AACTGGTAAT AACTGGTGAG GGGATAACCA CTGCTATGAA AGGTAATGAT TAGGTATTGT ACCGAGAAAC GGTGTTGATA

1361 CTCTATTGGC TATATGCCAA TACTCTGTCC TTCAGAGACT GACACGGACT CTGTATTTTT ACAGGATGGG GTCCATTTAT
GAGATAACCG ATATACGGTT ATGAGACAGG AAGTCTCTGA CTGTGCCTGA GACATAAAAA TGTCCTACCC CAGGTAAATA

FIGURE 5 - Page 2

1441 TATTTACAAA TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCAGTTT TTATTAAACA TAGCGTGGGA TCTCCGACAT
ATAAATGTTT AAGTGTATAT GTTGTGCGG CAGGGGGCAC GGGCGTCAAA AATAATTGT ATCGCACCT AGAGGCTGTA

1521 CTCGGGTACG TGTTCCGGAC ATGGGCTCTT CTCCGGTAGC GCGGAGCTT CCACATCCGA GCCCTGGTCC CATCCGTCCA
GAGCCCATGC ACAAGGCCG TACCCGAGAA GAGGCCATCG CCGCCTCGAA GGTGTAGGCT CGGGACCAGG GTAGGCAGGT

1601 GCGGCTCATG GTCGCTCGGC AGCTCCTTGC TCCTAACAGT GGAGGCCAGA CTTAGGCACA GCACAATGCC CACCACCACC
CGCCGAGTAC CAGCGAGCCG TCGAGGAACG AGGATTGTCA CCTCCGGTCT GAATCCGTGT CGTGTTACGG GTGGTGGTGG

1681 AGTGTGCCGC ACAAGGCCGT GGCGGTAGGG TATGTGTCTG AAAATGAGCT CGGAGATTGG GCTCGCACCT GGACGCAGAT
TCACACGGCG TGTTCCGGCA CCGCCATCCC ATACACAGAC TTTTACTCGA GCCTCTAACC CGAGCGTGGG CCTGCGTCTA

1761 GGAAGACTTA AGGCAGCGGC AGAAGAAGAT GCAGGCAGCT GAGTTGTTGT ATTCTGATAA GAGTCAGAGG TAACTCCCCT
CCTTCTGAAT TCCGTCGCCG TCTTCTTCTA CGTCCGTCGA CTCAACAACA TAAGACTATT CTCAGTCTCC ATTGAGGGCA

1841 TGCGGTGCTG TTAACGGTGG AGGGCAGTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG CGCCACCAGA CATAATAGCT
ACGCCACGAC AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC GCGGTGGTCT GTATTATCGA

+2 EcoRI M A A
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1921 GACAGACTAA CAGACTGTTT CTTTCCATGG GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCTGCAT  
CTGTCTGATT GTCTGACAAG GAAAGGTACC CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGACGTA

+2 Y A A Q G Y K V L V L N P S V A A T L G F G A Y M S K  
2001 ATGCAGCTCA GGGCTATAAG GTGCTAGTAC TCAACCCCTC TGTTGCTGCA AACTGGGCT TTGGTGCTTA CATGTCCAAG  
TACGTCGAGT CCCGATATTC CACGATCATG AGTTGGGGAG ACAACGACGT TGTGACCCGA AACCACGAAT GTACAGGTTC

+2 A H G I D P N I R T G V R T I T T G S P I T Y S T Y G  
2081 GCTCATGGGA TCGATCCTAA CATCAGGACC GGGGTGAGAA CAATTACCAC TGGCAGCCCC ATCAGTACT CCACCTACGG  
CGAGTACCCT AGCTAGGATT GTAGTCCTGG CCCCCTCTT GTTAATGGTG ACCGTCGGGG TAGTGATGA GGTGGATGCC

+2 K F L A D G G C S G G A Y D I I I C D E C H S T D A  
2161 CAAGTTCCTT GCCGACGGCG GGTGCTCGGG GGGCGCTTAT GACATAATAA TTTGTGACGA GTGCCACTCC ACGGATGCCA  
GTTCAAGGAA CGGCTGCCGC CCACGAGCCC CCCGCAATA CTGTATTATT AAACACTGCT CACGGTGAGG TGCCTACGGT

+2 T S I L G I G T V L D Q A E T A G A R L V V L A T A T  
2241 CATCCATCTT GGGCATTGGC ACTGTCCTTG ACCAAGCAGA GACTGCGGGG GCGAGACTGG TTGTGCTCGC CACCGCCACC  
GTAGGTAGAA CCCGTAACCG TGACAGGAAC TGGTTCGTCT CTGACGCCCC CGCTCTGACC AACACGAGCG GTGGCGGTGG

+2 P P G S V T V P H P N I E E V A L S T T G E I P F Y G  
2321 CCTCCGGGCT CCGTCACTGT GCCCCATCCC AACATCGAGG AGGTTGCTCT GTCCACCACC GGAGAGATCC CTTTTTACGG  
GGAGGCCCGA GGCAGTGACA CGGGGTAGGG TTGTAGCTCC TCCAACGAGA CAGGTGGTGG CCTCTCTAGG GAAAAATGCC

+2 K A I P L E V I K G G R H L I F C H S K K K C D E L  
2401 CAAGGCTATC CCCCTCGAAG TAATCAAGGG GGGGAGACAT CTCATCTTCT GTCATTCAAA GAAGAAGTGC GACGAACCTCG  
GTTCCGATAG GGGGAGCTTC ATTAGTTCCC CCCCTCTGTA GAGTAGAAGA CAGTAAGTTT CTCTTACG CTGCTTGAGC

+2 A A K L V A L G I N A V A Y Y R G L D V S V I P T S G  
2481 CCGCAAAGCT GGTGCGATTG GGCATCAATG CCGTGGCCTA CTACCGCGGT CTTGACGTGT CCGTCATCCC GACCAGCGGG  
GGCGTTTCGA CCAGCGTAAC CCGTAGTTAC GGCACCGGAT GATGGCGCCA GAACTGCACA GGCAGTAGGG CTGGTCGCCG

+2 D V V V V A T D A L M T G Y T G D F D S V I D C N T C  
2561 GATGTTGTCG TCGTGGCAAC CGATGCCCTC ATGACCGGCT ATACCGGCGA CTTGACTCG GTGATAGACT GCAATACGTG  
CTACAACAGC AGCACCGTTG GCTACGGGAG TACTGGCCGA TATGGCCGCT GAAGCTGAGC CACTATCTGA CGTTATGCAC

## FIGURE 5 - Page 3

+2 V T Q T V D F S L D P T F T I E T I T L P Q D A V S  
 2641 TGTCACCCAG ACAGTCGATT TCAGCCTTGA CCCTACCTTC ACCATTGAGA CAATCACGCT CCCCCAAGAT GCTGTCTCCC  
 ACAGTGGGTC TGTCAGCTAA AGTCGGAAGT GGGATGGAAG TGGTAACTCT GTTAGTGCGA GGGGGTTCTA CGACAGAGGG

+2 R T Q R R G R T G R G K P G I Y R F V A P G E R P S G  
 2721 GCACTCAACG TCGGGGCAGG ACTGGCAGGG GGAAGCCAGG CATCTACAGA TTTGTGGCAC CGGGGGAGCG CCCCTCCGGC  
 CGTGAGTTGC AGCCCCGTCC TGACCGTCCC CCTTCGGTCC GTAGATGTCT AAACACCGTG GCCCCTCGC GGGGAGGCCG

+2 M F D S S V L C E C Y D A G C A W Y E L T P A E T T V  
 2801 ATGTTGCACT CGTCCGTCCT CTGTGAGTGC TATGACGCAG GCTGTGCTTG GTATGAGCTC ACGCCCGCCG AGACTACAGT  
 TACAAGCTGA GCAGGCAGGA GAACTCACG ATACTGCGTC CGACACGAAC CATACTCGAG TCGGGGCGGC TCTGATGTCA

+2 R L R A Y M N T P G L P V C Q D H L E F W E G V F T  
 2881 TAGGCTACGA GCGTACATGA ACACCCCGGG GCTTCCCGTG TGCCAGGACC ATCTTGAATT TTGGGAGGGC GTCTTTACAG  
 ATCCGATGCT CGCATGTACT TGTGGGGCCC CGAAGGGCAC ACGGTCCTGG TAGAACTTAA AACCTTCCCG CAGAAATGTC

+2 G L T H I D A H F L S Q T K Q S G E N L P Y L V A Y Q  
 2961 GCCTCACTCA TATAGATGCC CACTTTCTAT CCCAGACAAA GCAGAGTGGG GAGAACCTTC CTTACCTGGT AGCGTACCAA  
 CGGAGTGAGT ATATCTACGG GTGAAAGATA GGGTCTGTTT CGTCTCACCC CTCTTGGAAG GAATGGACCA TCGCATGGTT

+2 A T V C A R A Q A P P P S W D Q M W K C L I R L K P T  
 3041 GCCACCGTGT GCGCTAGGGC TCAAGCCCCT CCCCCATCGT GGGACCAGAT GTGGAAGTGT TTGATTGCGC TCAAGCCAC  
 CGGTGGCACA CGCGATCCCG AGTTCGGGGA GGGGGTAGCA CCCTGGTCTA CACCTTCACA AACTAAGCGG AGTTCGGGTG

+2 L H G P T P L L Y R L G A V Q N E I T L T H P V T K  
 3121 CCTCCATGGG CCAACACCCC TGCTATACAG ACTGGGCGCT GTTCAGAATG AAATCACCTT GACGCACCCA GTCACCAAAT  
 GGAGGTACCC GGTGTGGGG ACGATATGTC TGACCCGCGA CAAGTCTTAC TTTAGTGGGA CTGCGTGGGT CAGTGGTTTA

+2 Y I M T C M S A D L E V V T S T W V L V G G V L A A L  
 3201 ACATCATGAC ATGCATGTCG GCCGACCTGG AGGTCGTCAC GAGCACCTGG GTGCTCGTTG GCGGCGTCTT GGCTGCTTTG  
 TGTAAGTACTG TACGTACAGC CGGCTGGACC TCCAGCAGTG CTCGTGGACC CACGAGCAAC CGCCGCAGGA CCGACGAAAC

+2 A A Y C L S T G C V V I V G R V V L S G K P A I I P D  
 3281 GCCGCGTATT GCCTGTCAAC AGGCTGCGTG GTCATAGTGG GCAGGGTCTG CTTGTCCGGG AAGCCGGCAA TCATACCTGA  
 CGGCGCATAA CGGACAGTTG TCCGACGCAC CAGTATCACC CGTCCCAGCA GAACAGGCC TTCGGCCGTT AGTATGGACT

+2 R E V L Y R E F D E M E E C S Q H L P Y I E Q G M M  
 3361 CAGGGAAGTC CTCTACCGAG AGTTCGATGA GATGGAAGAG TGCTCTCAGC ACTTACCGTA CATCGAGCAA GGGATGATGC  
 GTCCCTTCAG GAGATGGCTC TCAAGCTACT CTACCTTCTC ACGAGAGTCG TGAATGGCAT GTAGCTCGTT CCCTACTACG

+2 L A E Q F K Q K A L G L L Q T A S R Q A E V I A P A V  
 3441 TCGCCGAGCA GTTCAAGCAG AAGGCCCTCG GCCTCCTGCA GACCGCGTCC CGTCAGGCAG AGGTTATCGC CCCTGCTGTC  
 AGCGGCTCGT CAAGTTCGTC TTCCGGGAGC CGGAGGACGT CTGGCGCAGG GCAGTCCGTC TCCAATAGCG GGGACGACAG

+2 Q T N W Q K L E T F W A K H M W N F I S G I Q Y L A G  
 3521 CAGACCAACT GGCAAAACT CGAGACCTTC TGGGCGAAGC ATATGTGGAA CTTATCAGT GGGATACAA ACTTGGCGGG  
 GTCTGGTTGA CCGTTTTTGA GCTCTGGAAG ACCCGCTTCG TATACACCTT GAAGTAGTCA CCCTATGTTA TGAACCGCCC

+2 L S T L P G N P A I A S L M A F T A A V T S P L T T  
 3601 CTTGTCAACG CTGCTGGTA ACCCGGCCAT TGCTTCATTG ATGGCTTTTA CAGCTGCTGT CACCAGCCCA CTAACCACTA  
 GAACAGTTGC GACGGACCAT TGGGGCGGTA ACGAAGTAAC TACCGAAAAT GTCGACGACA GTGGTCGGGT GATTGGTGAT

+2 S Q T L L F N I L G G W V A A Q L A A P G A A T A F V  
 3681 GCCAAACCCT CCTCTTCAAC ATATTGGGGG GGTGGGTGGC TGCCAGCTC GCCGCCCCG GTGCCGTAC TGCCTTTGTG  
 CGGTTTGGGA GGAGAAGTTG TATAACCCCC CCACCCACCG ACGGGTCGAG CGGCGGGGGC CACGGCGATG ACGGAAACAC

## FIGURE 5 - Page 4

+2 G A G L A G A A I G S V G L G K V L I D I L A G Y G A  
 3761. GGCCTGGCT TAGCTGGCGC CGCCATCGGC AGTGTGGAC TGGGGAAGGT CCTCATAGAC ATCCTTGACG GGTATGGCGC  
 CCCGACCGA ATCGACCGC GCGGTAGCCG TCACAACCTG ACCCCTTCCA GGAGTATCTG TAGGAACGTC CCATACCGC

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+2 G V A G A L V A F K I M S G E V P S T E D L V N L L  
 3841 GGGCTGGCG GGAGCTCTTG TGGCATTCAA GATCATGAGC GGTGAGGTCC CCTCCACGGA GGACCTGGTC AATCTACTGC  
 CCCGACCGC CCTCGAGAAC ACCGTAAGTT CTAGTACTCG CCACTCCAGG GGAGGTGCCT CCTGGACCAG TTAGATGACG

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+2 P A I L S P G A L V V G V V C A A I L R R H V G P G E  
 3921 CCGCCATCCT CTCGCCCCGA GCCCTCGTAG TCGGCGTGGT CTGTGCAGCA ATACTGCGCC GGCACGTTGG CCCGGGCGAG  
 GCGGCTAGGA GAGCGGGCCT CGGGAGCATC AGCCGCACCA GACACGTCGT TATGACGCGG CCGTGCAACC GGGCCCCGCT

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+2 G A V Q W M N R L I A F A S R G N H V S P T H Y V P E  
 4001 GGGCAGTGC AGTGGATGAA CCGGCTGATA GCCTTCGCCT CCCGGGGGAA CCATGTTTCC CCCACGCACT ACGTGCCGGA  
 CCCCCTCAG TCACCTACTT GGCGACTAT CGGAAGCGGA GGGCCCCCTT GGTACAAAGG GGTGCGTGA TGCACGGCCT

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+2 S D A A A R V T A I L S S L T V T Q L L R R L H Q W  
 4081 GAGCGATGCA GCTGCCCGC TCACTGCCAT ACTCAGCAGC CTCAGTGTA CCCAGTCCT GAGGCGACTG CACCACTGGA  
 CTCGCTACGT CGACGGGCGC AGTGACGGTA TGAGTCGTCG GAGTGACATT GGTGCGAGGA CTCCGCTGAC GTGGTCACCT

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+2 I S S E C T T P C S G S W L R D I W D W I C E V L S D  
 4161 TAAGCTCGGA GTGTACCACT CCATGTCCG GTTCCTGGCT AAGGGACATC TGGGACTGGA TATGCGAGGT GTTGAGCGAG  
 ATTCGAGCCT CACATGGTGA GGTACGAGGC CAAGGACCGA TTCCCTGTAG ACCCTGACCT ATACGCTCCA CAACTCGTG

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+2 F K T W L K A K L M P Q L P G I P F V S C Q R G Y K G  
 BamHI  
 ~~~~~  
 4241 TTTAAGACCT GGCTAAAAGC TAAGCTCATG CCACAGCTGC CTGGGATCCC CTTTGTGTCC TGCCAGCGCG GGTATAAGGG
 AAATTCTGGA CCGATTTTCG ATTCGAGTAC GGTGTCGACG GACCCTAGGG GAAACACAGG ACGGTCGCGC CCATATTCCC

+2 V W R G D G I M H T R C H C G A E I T G H V K N G T
 4321 GGTCTGGCGA GGGGACGGCA TCATGCACAC TCGCTGCCAC TGTGGAGCTG AGATCACTGG ACATGTCAAA AACGGGACGA
 CCAGACCGCT CCCCTGCCGT AGTACGTGTG AGCGACGGTG ACACCTCGAC TCTAGTGACC TGTACAGTTT TTGCCCTGCT

+2 M R I V G P R T C R N M W S G T F P I N A Y T T G P C
 4401 TGAGGATCGT CGGTCCTAGG ACCTGCAGGA ACATGTGGAG TGGGACCTTC CCCATTAATG CCTACACCAC GGGCCCCCTGT
 ACTCCTAGCA GCCAGGATCC TGGACGTCCT TGTACACCTC ACCCTGGAAG GGGTAATTAC GGATGTGGTG CCCGGGGACA

+2 T P L P A P N Y T F A L W R V S A E E Y V E I R Q V G
 4481 ACCCCCCCTC CTGCGCCGAA CTACACGTTT GCGCTATGGA GGGTGTCTGC AGAGGAATAC GTGGAGATAA GGCAGGTGGG
 TGGGGGGAAG GACGCGGCTT GATGTGCAAG CGCGATACCT CCCACAGACG TCTCCTTATG CACCTCTATT CCGTCCACCC

+2 D F H Y V T G M T T D N L K C P C Q V P S P E F F T
 4561 GGACTTCCAC TACGTGACGG GTATGACTAC TGACAATCTT AAATGCCCCG GCCAGGTCCC ATCGCCCGAA TTTTTCACAG
 CCTGAAGGTG ATGCACTGCC CATACTGATG ACTGTTAGAA TTTACGGGCA CCGTCCAGGG TAGCGGGCTT AAAAAGTGTC

+2 E L D G V R L H R F A P P C K P L L R E E V S F R V G
 4641 AATTGGACGG GGTGCGCCTA CATAGTTTG CGCCCCCTG CAAGCCCTTG CTGCGGGAGG AGGTATCATT CAGAGTAGGA
 TTAACCTGCC CCACGCGGAT GTATCCAAAC GCGGGGGGAC GTTCGGGAAC GACGCCCTCC TCCATAGTAA GTCTCATCTT

+2 L H E Y P V G S Q L P C E P E P D V A V L T S M L T D
 4721 CTCCACGAAT ACCCGGTAGG GTCGCAATTA CCTTGCGAGC CCGAACCAGA CGTGGCCGTG TTGACGTCCA TGCTCACTGA
 GAGGTGCTTA TGGGCCATCC CAGCGTTAAT GGAACGCTCG GGCTTGGCTT GCACCGGCAC AACTGCAGGT ACGAGTGACT

+2 P S H I T A E A A G R R L A R G S P P S V A S S S A
 4801 TCCCTCCCAT ATAACAGCAG AGGCGGGCCG GCGAAGGTTG GCGAGGGGAT CACCCCCCTC TGTGGCCAGC TCCTCGGCTA
 AGGGAGGGTA TATTGTCGTC TCCGCCGGCC CGCTTCCAAC CGCTCCCTTA GTGGGGGGAG ACACCGGTG AGGAGCCGAT

00222T" 524T260

+2	S	Q	L	S	A	P	S	L	K	A	T	C	T	A	N	H	D	S	P	D	A	E	L	I	E	A	N
4881	GCCAGCTATC	CGCTCCATCT	CTCAAGGCAA	CTTGACACCGC	TAACCATGAC	TCCCCTGATG	CTGAGCTCAT	AGAGGCCAAC	CGGTGATAG	GCGAGGTAGA	GAGTTCGGTT	GAACGTGGCG	ATTGGTACTG	AGGGGACTAC	GACTCGAGTA	TCTCCGGTTG											
+2	L	L	W	R	Q	E	M	G	G	N	I	T	R	V	E	S	E	N	K	V	V	I	L	D	S	F	D
4961	CTCCTATGGA	GGCAGGAGAT	GGGCGGCAAC	ATCACCAGGG	TTGAGTCAGA	AAACAAAGTG	GTGATTCTGG	ACTCCTTCGA	GAGGATACCT	CCGTCCTCTA	CCC GCCGTTG	TAGTGGTCCC	AACTCAGTCT	TTGTTTTCAC	CACTAAGACC	TGAGGAAGCT											
+2	P	L	V	A	E	E	D	E	R	E	I	S	V	P	A	E	I	L	R	K	S	R	R	F	A	Q	
5041	TCCGCTTGTTG	GCGGAGGAGG	ACGAGCGGGA	GATCTCCGTA	CCCGCAGAAA	TCTTGCGGAA	GTCTCGGAGA	TTCGCCCAGG	AGGCGAACAC	CGCCTCCTCC	TGCTCGCCCT	CTAGAGGCAT	GGGCGTCTTT	AGGACGCCTT	CAGAGCCTCT	AAGCGGGTCC											
+2	A	L	P	V	W	A	R	P	D	Y	N	P	P	L	V	E	T	W	K	K	P	D	Y	E	P	P	V
5121	CCCTGCCCCG	TTGGGCGCGG	CCGGACTATA	ACCCCCCGCT	AGTGGAGACG	TGGAAAAAGC	CCGACTACGA	ACCACCTGTG	GGGACGGGCA	AACCCGCGCC	GGCCTGATAT	TGGGGGGCGA	TCACCTCTGC	ACCTTTTTCG	GGCTGATGCT	TGGTGGACAC											
+2	V	H	G	C	P	L	P	P	P	K	S	P	P	V	P	P	P	R	K	K	R	T	V	V	L	T	E
5201	GTCCATGGCT	GCCCGCTTCC	ACCTCCAAAG	TCCCCTCCTG	TGCTCCGCC	TCGGAAGAAG	CGGACGGTGG	TCCTCACTGA	CAGGTACCGA	CGGGCGAAGG	TGGAGGTTTC	AGGGGAGGAC	ACGGAGGCGG	AGCCTTCTTC	GCCTGCCACC	AGGAGTGACT											
+2	S	T	L	S	T	A	L	A	E	L	A	T	R	S	F	G	S	S	S	T	S	G	I	T	G	D	
5281	ATCAACCCTA	TCTACTGCCT	TGGCCGAGCT	CGCCACCAGA	AGCTTTGGCA	GCTCCTCAAC	TTCCGGCATT	ACGGGCGACA	TAGTTGGGAT	AGATGACGGA	ACCGGCTCGA	GCGGTGGTCT	TCGAAACCGT	CGAGGAGTTG	AAGGCCGTAA	TGCCCGCTGT											
+2	N	T	T	T	S	S	E	P	A	P	S	G	C	P	P	D	S	D	A	E	S	Y	S	S	M	P	P
5361	ATACGACAAC	ATCCTCTGAG	CCCGCCCCCT	CTGGCTGCCC	CCCCGACTCC	GACGCTGAGT	CCTATTCTCT	CATGCCCCCC	TATGCTGTTG	TAGGAGACTC	GGGCGGGGAA	GACCGACGGG	GGGGCTGAGG	CTGCGACTCA	GGATAAGGAG	GTACGGGGGG											
+2	L	E	G	E	P	G	D	P	D	L	S	D	G	S	W	S	T	V	S	S	E	A	N	A	E	D	V
							BamHI																				
5441	CTGGAGGGGG	AGCCTGGGGA	TCCGGATCTT	AGCGACGGGT	CATGGTCAAC	GGTCAGTAGT	GAGGCCAACG	CGGAGGATGT	GACCTCCCCC	TCGGACCCCT	AGGCCTAGAA	TCGCTGCCCA	GTACCAGTTG	CCAGTCATCA	CTCCGGTTGC	GCCTCTTACA											
+2	V	C	C	S	M	S	Y	S	W	T	G	A	L	V	T	P	C	A	A	E	E	Q	K	L	P	I	
5521	CGTGTGCTGC	TCAATGTCTT	ACTCTTGGAC	AGGCGCACTC	GTCACCCCGT	GCGCCGCGGA	AGAACAGAAA	CTGCCCATCA	GCACACGACG	AGTTACAGAA	TGAGAACCTG	TCCGCGTGAG	CAGTGGGGCA	CGCGGCGCCT	TCTTGTCTTT	GACGGGTAGT											
+2	N	A	L	S	N	S	L	L	R	H	H	N	L	V	Y	S	T	T	S	R	S	A	C	Q	R	Q	K
5601	ATGCACTAAG	CAACTCGTTG	CTACGTCACC	ACAATTTGGT	GTATTCCACC	ACCTCAGCAG	GTGCTTGCCA	AAGGCAGAAG	TACGTGATTG	GTTGAGCAAC	GATGCAGTGG	TGTAAACCA	CATAAGGTGG	TGGAGTGCCT	CACGAACGGT	TTCCGTCTTC											
+2	K	V	T	F	D	R	L	Q	V	L	D	S	H	Y	Q	D	V	L	K	E	V	K	A	A	A	S	K
5681	AAAGTCACAT	TTGACAGACT	GCAAGTTCTG	GACAGCCATT	ACCAGGACGT	ACTCAAGGAG	GTAAAGCAG	CGGCGTCAAA	TTTCAGTGTA	AACTGTCTGA	CGTTCAAGAC	CTGTCCGTAA	TGGTCTGCA														

FIGURE 5 - Page 6

+2 R L I V F P D L G V R V C E K M A L Y D V V T K L P
 6001 TCGTCTCATC GTGTTCCCCG ATCTGGGCGT GCGCGTGTGC GAAAAGATGG CTTTGTACGA CGTGGTTACA AAGCTCCCT
 AGCAGAGTAG CACAAGGGGC TAGACCCGCA CGCGCACACG CTTTCTACC GAAACATGCT GCACCAATGT TTCGAGGGGA

+2 L A V M G S S Y G F Q Y S P G Q R V E F L V Q A W K S
 EcoRI
 ~~~~~  
 6081 TGGCCGTGAT GGAAGCTCC TACGGATTCC AATACTCACC AGGACAGCGG GTTGAATTCC TCGTGCAAGC GTGGAAGTCC  
 ACCGGCACTA CCCTTCGAGG ATGCTTAAGG TTATGAGTGG TCCTGTCGCC CAACTTAAGG AGCACGTTCC CACCTTCAGG

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+2 K K T P M G F S Y D T R C F D S T V T E S D I R T E E  
 6161 AAGAAAACCC CAATGGGGTT CTCGTATGAT ACCCGCTGCT TTGACTCCAC AGTCACTGAG AGCGACATCC GTACGGAGGA  
 TTCTTTTGGG GTTACCCCAA GAGCATACTA TGGGCGACGA AACTGAGGTG TCAGTGACTC TCGTGTAGG CATGCCTCT

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+2 A I Y Q C C D L D P Q A R V A I K S L T E R L Y V G  
 6241 GGCAATCTAC CAATGTTGTG ACCTCGACCC CCAAGCCCGC GTGGCCATCA AGTCCCTCAC CGAGAGGCTT TATGTTGGGG  
 CCGTTAGATG GTTACAACAC TGGAGCTGGG GGTTGGGGCG CACCGGTAGT TCAGGGAGTG GCTCTCCGAA ATACAACCC

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+2 G P L T N S R G E N C G Y R R C R A S G V L T T S C G  
 6321 GCCCTCTTAC CAATTCAAGG GGGGAGAACT GCGGCTATCG CAGGTGCCGC GCGAGCGGCG TACTGACAAC TAGCTGTGGT  
 CGGGAGAATG GTTAAGTTC CCCCTCTTGA CGCCGATAGC GTCCACGGCG CGCTCGCCGC ATGACTGTTG ATCGACACCA

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+2 N T L T C Y I K A R A A C R A A G L Q D C T M L V C G  
 6401 AACACCCTCA CTTGCTACAT CAAGGCCCGG GCAGCCTGTC GAGCCGCAGG GCTCCAGGAC TGCAACATGC TCGTGTGTGG  
 TTGTGGGAGT GAACGATGTA GTTCCGGGCC CGTCGGACAG CTCGGCGTCC CGAGGTCTTG ACGTGGTACG AGCACACACC

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+2 D D L V V I C E S A G V Q E D A A S L R A F T E A M  
 6481 CGACGACTTA GTCGTTATCT GTGAAAGCGC GGGGGTCCAG GAGGACGCGG CGAGCCTGAG AGCCTTCACG GAGGCTATGA  
 GCTGCTGAAT CAGCAATAGA CACTTTCGCG CCCCCAGGTC CTCCTGCGCC GCTCGGACTC TCGAAGTGC CTCGGATACT

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+2 T R Y S A P P G D P P Q P E Y D L E L I T S C S S N V  
 6561 CCAGGTACTC CGCCCCCCT GGGGACCCCC CACAACCAGA ATACGACTTG GAGCTCATAA CATCATGCTC CTCCAACGTG  
 GGTCCATGAG GCGGGGGGGA CCCCTGGGGG GTGTTGGTCT TATGCTGAAC CTCGAGTATT GTAGTACGAG GAGGTTGCAC

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+2 S V A H D G A G K R V Y Y L T R D P T T P L A R A A W  
 6641 TCAGTCGCCC ACGACGGCGC TGGAAAGAGG GTCTACTACC TCACCCGTGA CCCTACAACC CCCCTCGCGA GAGCTGCGTG  
 AGTCAGCGGG TGCTGCCGCG ACCTTCTCC CAGATGATGG AGTGGGCACT GGGATGTTGG GGGGAGCGCT CTCGACGCAC

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+2 E T A R H T P V N S W L G N I I M F A P T L W A R M  
 6721 GGAGACAGCA AGACACACTC CAGTCAATTC CTGGCTAGGC AACATAATCA TGTTTGCCCC CACACTGTGG GCGAGGATGA  
 CCTCTGTCGT TCTGTGTGAG GTCAGTTAAG GACCGATCCG TTGTATTAGT ACAAACGGGG GTGTGACACC CGCTCCTACT

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+2 I L M T H F F S V L I A R D Q L E Q A L D C E I Y G A  
 6801 TACTGATGAC CCATTTCTTT AGCGTCCTTA TAGCCAGGGA CCAGCTTGAA CAGGCCCTCG ATTGCGAGAT CTACGGGGCC  
 ATGACTACTG GGTAAAGAAA TCGCAGGAAT ATCGGTCCCT GGTGCAACTT GTCCGGGAGC TAACGCTCTA GATGCCCGGG

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+2 C Y S I E P L D L P P I I Q R L H G L S A F S L H S Y  
 6881 TGCTACTCCA TAGAACCCTT GGATCTACCT CCAATCATTC AAAGACTCCA TGGCCTCAGC GCATTTTCAC TCCACAGTTA  
 ACGATGAGGT ATCTTGGTGA CCTAGATGGA GGTTAGTAAG TTTCTGAGGT ACCGGAGTCG CGTAAAGTG AGGTGTCAAT

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+2 S P G E I N R V A A C L R K L G V P P L R A W R H R  
 6961 CTCTCCAGGT GAAATCAATA GGGTGGCCGC ATGCTCAGA AAAGTGGGG TACCGCCCTT GCGAGCTTGG AGACACCGGG  
 GAGAGGTCCA CTTTAGTTAT CCCACCGCGG TACGAGTCT TTTGAACCC ATGGCGGGAA CGCTCGAACC TCTGTGGCCC

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+2 A R S V R A R L L A R G G R A A I C G K Y L F N W A V  
 7041 CCCGAGCGT CCGCGCTAGG CTTCTGGCCA GAGGAGGCAG GGCTGCCATA TGTGGCAAGT ACCTCTTCAA CTGGGCAGTA  
 GGGCCTCGCA GCGCGATCC GAAGACCGGT CTCCTCCGTC CCGACGGTAT ACACGGTTCA TGGAGAAGTT GACCCGTCAT

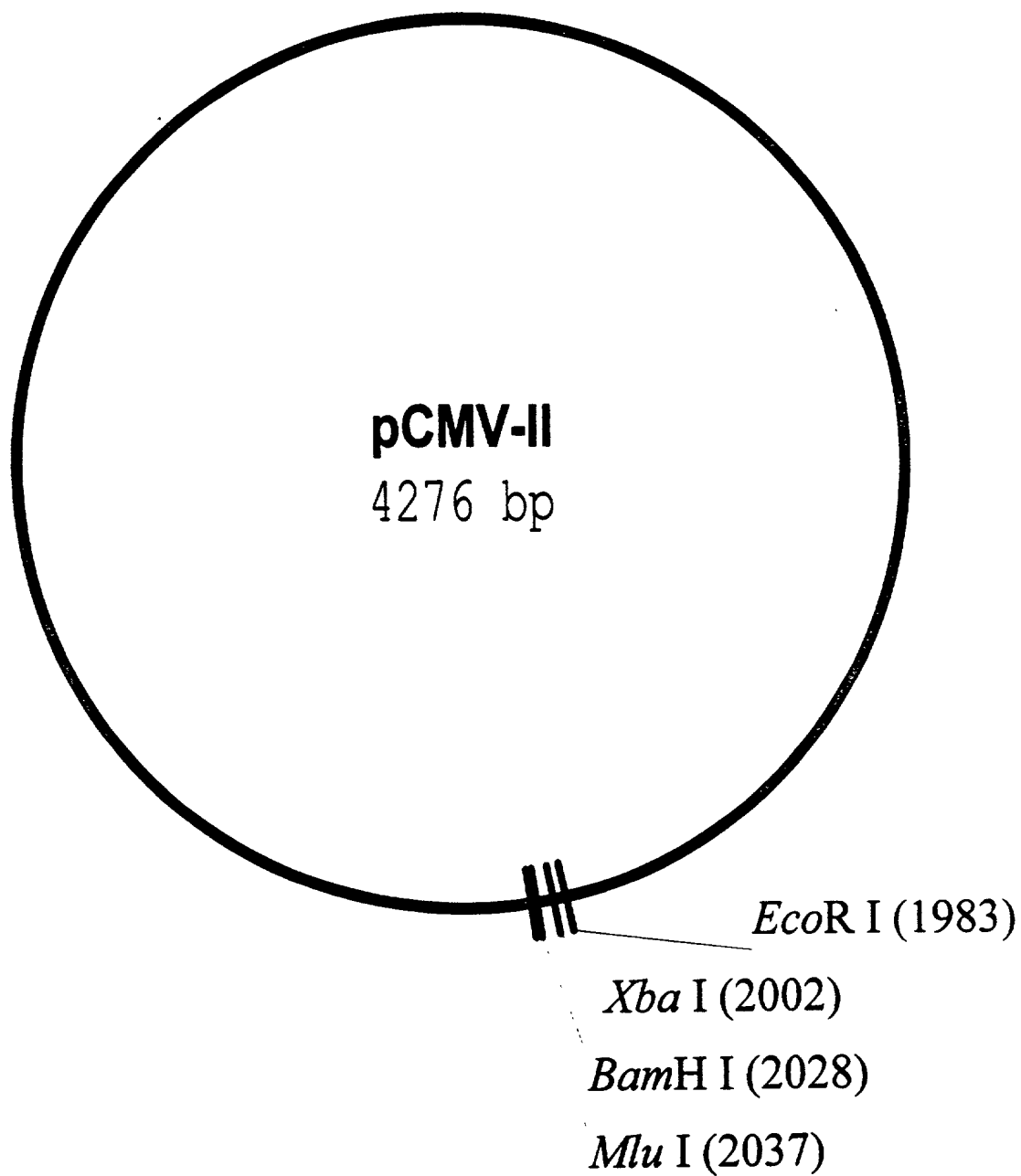
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|      |    |            |             |             |            |            |             |            |            |            |            |            |             |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
|------|----|------------|-------------|-------------|------------|------------|-------------|------------|------------|------------|------------|------------|-------------|------------|------------|-------------|------------|---|---|---|---|---|---|---|---|---|---|---|
|      | +2 | R          | T           | K           | L          | K          | L           | T          | P          | I          | A          | A          | G           | G          | Q          | L           | D          | L | S | G | W | F | T | A | G | Y | S | G |
| 7121 |    | AGAACAAAGC | TCAAACCTCAC | TCCAATAGCG  | GCCGCTGGCC | AGCTGGACTT | GTCCGGCTGG  | TTCACGGCTG | GCTACAGCGG | TCTTGTTCG  | AGTTTGAGTG | AGGTTATCGC | CGGCGACCGG  | TCGACCTGAA | CAGGCCGACC | AAGTGCCGAC  | CGATGTCGCC |   |   |   |   |   |   |   |   |   |   |   |
|      | +2 | G          | D           | I           | Y          | H          | S           | V          | S          | H          | A          | R          | P           | R          | W          | I           | W          | F | C | L | L | L | L | A | A | G | V |   |
| 7201 |    | GGGAGACATT | TATCACAGCG  | TGTCCTCATGC | CCGGCCCCGC | TGGATCTGGT | TTTGCCCTACT | CCTGCTTGCT | GCAGGGGTAG | CCCTCTGTAA | ATAGTGTGCG | ACAGAGTACG | GGCCGGGGCG  | ACCTAGACCA | AAACGGATGA | GGACGAACGA  | CGTCCCCATC |   |   |   |   |   |   |   |   |   |   |   |
|      | +2 | G          | I           | Y           | L          | L          | P           | N          | R          |            |            |            |             |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| 7281 |    | GCATCTACCT | CCTCCCCAAC  | CGATGAAGGT  | TGGGGTAAAC | ACTCCGGCCT | AAAAAAAAAA  | AAAAATCTAG | AAAGGCGCG  | CGTAGATGGA | GGAGGGGTG  | GCTACTTCCA | ACCCCATTTG  | TGAGGCCGGA | TTTTTTTTTT | TTTTTAGATC  | TTTCCGCGCG |   |   |   |   |   |   |   |   |   |   |   |
|      |    |            | BamHI       |             | MluI       |            |             |            |            |            |            |            |             |            |            |             |            |   |   |   |   |   |   |   |   |   |   |   |
| 7361 |    | CAAGATATCA | AGGATCCACT  | ACGCGTTAGA  | GCTCGCTGAT | CAGCCTCGAC | TGTGCCTTCT  | AGTTGCCAGC | CATCTGTTGT | GTTCTATAGT | TCCTAGGTGA | TGCGCAATCT | CGAGCGACTA  | GTCGGAGCTG | ACACGGAAGA | TCAACGGTCG  | GTAGACAACA |   |   |   |   |   |   |   |   |   |   |   |
| 7441 |    | TTGCCCTCC  | CCCGTGCCTT  | CCTTGACCCT  | GGAAGGTGCC | ACTCCCACTG | TCCTTTCCTA  | ATAAAATGAG | GAAATTGCAT | AACGGGGAGG | GGGCACGGAA | GGAAGTGGGA | CCTTCCACGG  | TGAGGGTGAC | AGGAAAGGAT | TATTTTACTC  | CTTTAACGTA |   |   |   |   |   |   |   |   |   |   |   |
| 7521 |    | CGCATTGTCT | GAGTAGGTGT  | CATTCTATTC  | TGGGGGGTGG | GGTGGGGCAG | GACAGCAAGG  | GGGAGGATTG | GGAAGACAAT | GCGTAACAGA | CTCATCCACA | GTAAGATAAG | ACCCCCACC   | CCACCCCGTC | CTGTCGTTCC | CCCTCCTAAC  | CCTTCTGTTA |   |   |   |   |   |   |   |   |   |   |   |
| 7601 |    | AGCAGGCATG | CTGGGGAGCT  | CTTCCGCTTC  | CTCGCTCACT | GACTCGTGC  | GCTCGGTCGT  | TCGGCTGCGG | CGAGCGGTAT | TCGTCCGTAC | GACCCCTCGA | GAAGGCGAAG | GAGCGAGTGA  | CTGAGCGACG | CGAGCCAGCA | AGCCGACGCC  | GCTCGCCATA |   |   |   |   |   |   |   |   |   |   |   |
| 7681 |    | CAGCTCACTC | AAAGGCGGTA  | ATACGGTTAT  | CCACAGAATC | AGGGGATAAC | GCAGGAAAGA  | ACATGTGAGC | AAAAGGCCAG | GTCGAGTGAG | TTTCCGCCAT | TATGCCAATA | GGTGCTTAG   | TCCCCTATTG | CGTCCTTTCT | TGTACACTCG  | TTTTCCGGTC |   |   |   |   |   |   |   |   |   |   |   |
| 7761 |    | CAAAAGGCCA | GGAACCGTAA  | AAAGGCCGCG  | TTGTGGCGT  | TTTTCCATAG | GCTCCGCCCC  | CCTGACGAGC | ATCACAAAAA | GTTTTCCGGT | CCTTGGCATT | TTTCCGGCGC | AACGACCGCA  | AAAAGGTATC | CGAGGCGGGG | GGACTGCTCG  | TAGTGTTTTT |   |   |   |   |   |   |   |   |   |   |   |
| 7841 |    | TCGACGCTCA | AGTCAGAGGT  | GGCGAAACCC  | GACAGGACTA | TAAAGATACC | AGGCGTTTCC  | CCCTGGAAGC | TCCCTCGTGC | AGTGCGAGT  | TCAGTCTCCA | CCGCTTTGGG | CTGTCTGAT   | ATTTCTATGG | TCCGCAAAGG | GGGACCTTCG  | AGGGAGCACG |   |   |   |   |   |   |   |   |   |   |   |
| 7921 |    | GCTCTCCTGT | TCCGACCCTG  | CCGCTTACCG  | GATACCTGTC | CGCCTTTCTC | CCTTCGGGAA  | CGGTGGCGCT | TTCTCAATGC | CGAGAGGACA | AGGCTGGGAC | GGCGAATGGC | CTATGGACAG  | GCGGAAAGAG | GGAAGCCCTT | CGCACC CGCA | AAGAGTTACG |   |   |   |   |   |   |   |   |   |   |   |
| 8001 |    | TCACGCTGTA | GGTATCTCAG  | TTCGGTGTAG  | GTCGTTGCT  | CCAAGCTGGG | CTGTGTGCAC  | GAACCCCCCG | TTCAGCCCGA | AGTGCGACAT | CCATAGAGTC | AAGCCACATC | CAGCAAGCGA  | GGTTCGACCC | GACACACGTG | CTTGGGGGGC  | AAGTCGGGCT |   |   |   |   |   |   |   |   |   |   |   |
| 8081 |    | CCGCTGCGCC | TTATCCGGTA  | ACTATCGTCT  | TGAGTCCAAC | CCGGTAAGAC | ACGACTTATC  | GCCACTGGCA | GCAGCCACTG | GGCGACGCGG | AATAGGCCAT | TGATAGCAGA | ACTCAGGTTG  | GGCCATTCTG | TGCTGAATAG | CGGTGACCGT  | CGTCGGTGAC |   |   |   |   |   |   |   |   |   |   |   |
| 8161 |    | GTAACAGGAT | TAGCAGAGCG  | AGGTATGTAG  | GCGGTGCTAC | AGAGTTCTTG | AAGTGGTGCG  | CTAACTACGG | CTACACTAGA | CATTGTCCTA | ATCGTCTCGC | TCCATACATC | CGCCACGATG  | TCTCAAGAAC | TTCACCACCG | GATTGATGCC  | GATGTGATCT |   |   |   |   |   |   |   |   |   |   |   |
| 8241 |    | AGGACAGTAT | TTGGTATCTG  | CGCTCTGCTG  | AAGCCAGTTA | CCTTCGGAAA | AAGAGTTGGT  | AGCTCTTGAT | CCGGCAAACA | TCCTGTCATA | AACCATAGAC | GCGAGACGAC | TTCCGGTCAAT | GGAAGCCTTT | TTCTCAACCA | TCGAGAACTA  | GGCCGTTTGT |   |   |   |   |   |   |   |   |   |   |   |
| 8321 |    | AACCACCGCT | GGTAGCGGTG  | GT TTTTTTGT | TTGCAAGCAG | CAGATTACGC | GCAGAAAAAA  | AGGATCTCAA | GAAGATCCTT | TTGGTGGCGA | CCATCGCCAC | CAAAAAAACA | AACGTTCTGC  | GTCTAATGCG | CGTCTTTTTT | TCCTAGAGTT  | CTTCTAGGAA |   |   |   |   |   |   |   |   |   |   |   |

**FIGURE 5 - Page 8**

|      |                           |                           |                          |                          |                          |                          |                          |                          |
|------|---------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| 8481 | ATCTTACACCT<br>TAGAAGTGGG | AGATCCTTTT<br>TCTAGGAAAA  | AAATTAAAAA<br>TTTAATTTTT | TGAAGTTTTA<br>ACTTCAAAAT | AATCAATCTA<br>TTAGTTAGAT | AAGTATATAT<br>TTCATATATA | GAGTAAACTT<br>CTCATTGAA  | GGTCTGACAG<br>CCAGACTGTC |
| 8561 | TTACCAATGC<br>AATGGTTACG  | TTAATCAGTG<br>AATTAGTCAC  | AGGCACCTAT<br>TCCGTGGATA | CTCAGCGATC<br>GAGTCGCTAG | TGTCTATTTT<br>ACAGATAAAG | GTTCATCCAT<br>CAAGTAGGTA | AGTTGCCTGA<br>TCAACGGACT | CTCCCGTCG<br>GAGGGGCAGC  |
| 8641 | TGTAGATAAC<br>ACATCTATTG  | TACGATACGG<br>ATGCTATGCC  | GAGGGCTTAC<br>CTCCCGAATG | CATCTGGCCC<br>GTAGACCGGG | CAGTGCTGCA<br>GTCACGACGT | ATGATACCGC<br>TACTATGGCG | GAGACCCACG<br>CTCTGGGTGC | CTCACCGGCT<br>GAGTGGCCGA |
| 8721 | CCAGATTTAT<br>GGTCTAAATA  | CAGCAATAAA<br>GTCGTTATTT  | CCAGCCAGCC<br>GGTCGGTCGG | GGAAGGGCCG<br>CCTTCCCGGC | AGCGCAGAAG<br>TCGCGTCTTC | TGGTCCTGCA<br>ACCAGGACGT | ACTTTATCCG<br>TGAAATAGGC | CCTCCATCCA<br>GGAGGTAGGT |
| 8801 | GTCTATTAAT<br>CAGATAATTA  | TGTTGCCGGG<br>ACAACGGCCC  | AAGCTAGAGT<br>TTCGATCTCA | AAGTAGTTCG<br>TTCATCAAGC | CCAGTTAATA<br>GGTCAATTAT | GTTTGCGCAA<br>CAAACGCGTT | CGTTGTTGCC<br>GCAACAACGG | ATTGCTACAG<br>TAACGATGTC |
| 8881 | GCATCGTGGT<br>CGTAGCACCA  | GTCACGCTCG<br>CAGTGCGAGC  | TCGTTTGGTA<br>AGCAAACCAT | TGGCTTCATT<br>ACCGAAGTAA | CAGCTCCGGT<br>GTCGAGGCCA | TCCCAACGAT<br>AGGGTTGCTA | CAAGGCGAGT<br>GTTCCGCTCA | TACATGATCC<br>ATGTACTAGG |
| 8961 | CCCATGTTGT<br>GGGTACAACA  | GCAAAAAAGC<br>CGTTTTTTCG  | GGTTAGCTCC<br>CCAATCGAGG | TTCGGTCCCT<br>AAGCCAGGAG | CGATCGTTGT<br>GCTAGCAACA | CAGAAGTAAG<br>GTCTTCATT  | TGGCCGCAG<br>AACC GGCGTC | TGTTATCACT<br>ACAATAGTGA |
| 9041 | CATGGTTATG<br>GTACCAATAC  | GCAGCACTGC<br>CGTCGTGACG  | ATAATTCTCT<br>TATTAAGAGA | TACTGTCATG<br>ATGACAGTAC | CCATCCGTAA<br>GGTAGGCATT | GATGCTTTTC<br>CTACGAAAAG | TGTGACTGGT<br>ACACTGACCA | GAGTACTCAA<br>CTCATGAGTT |
| 9121 | CCAAGTCATT<br>GGTTCAGTAA  | CTGAGAATAG<br>GACTCTTATC  | TGTATGCGGC<br>ACATACGCCG | GACCGAGTTG<br>CTGGCTCAAC | CTCTTGCCCG<br>GAGAACGGGC | GCGTCAATAC<br>CGCAGTTATG | GGGATAATAC<br>CCCTATTATG | CGCGCCACAT<br>GCGCGGTGTA |
| 9201 | AGCAGAACTT<br>TCGTCTTGAA  | TAAAAAGTGCT<br>ATTTTCACGA | CATCATTGGA<br>GTAGTAACCT | AAACGTTCTT<br>TTTGCAAGAA | CGGGGCGAAA<br>GCCCCGCTTT | ACTCTCAAGG<br>TGAGAGTTCC | ATCTTACCGC<br>TAGAATGGCG | TGTTGAGATC<br>ACAACCTAG  |
| 9281 | CAGTTCGATG<br>GTCAAGCTAC  | TAACCCACTC<br>ATTGGGTGAG  | GTGCACCCAA<br>CACGTGGGTT | CTGATCTTCA<br>GACTAGAAGT | GCATCTTTTA<br>CGTAGAAAAT | CTTTCACCAG<br>GAAAGTGGTC | CGTTTCTGGG<br>GCAAAGACCC | TGAGCAAAAA<br>ACTCGTTTTT |
| 9361 | CAGGAAGGCA<br>GTCCTTCCGT  | AAATGCCGCA<br>TTTACGGCGT  | AAAAAGGGAA<br>TTTTTCCCTT | TAAGGGCGAC<br>ATTCCCGCTG | ACGGAAATGT<br>TGCCTTTACA | TGAATACTCA<br>ACTTATGAGT | TACTCTTCCT<br>ATGAGAAGGA | TTTTCAATAT<br>AAAAGTTATA |
| 9441 | TATTGAAGCA<br>ATAACTTCGT  | TTTATCAGGG<br>AAATAGTCCC  | TTATTGTCTC<br>AATAACAGAG | ATGAGCGGAT<br>TACTCGCCTA | ACATATTTGA<br>TGTATAAACT | ATGTATTTAG<br>TACATAAATC | AAAAATAAAC<br>TTTTTATTTG | AAATAGGGGT<br>TTTATCCCCA |
| 9521 | TCCGCGCACA<br>AGGCGCGTGT  | TTTCCCCGAA<br>AAAGGGGCTT  | AAGTGCCACC<br>TTCACGGTGG | TGACGTCTAA<br>ACTGCAGATT | GAAACCATTA<br>CTTTGGTAAT | TTATCATGAC<br>AATAGTACTG | ATTAACCTAT<br>TAATTGGATA | AAAAATAGGC<br>TTTTTATCCG |
| 9601 | GTATCACGAG<br>CATAGTGCTC  | GCCCTTTCGT<br>CGGGAAAGCA  | C<br>G                   |                          |                          |                          |                          |                          |

FIGURE 6



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## FIGURE 7 - Page 1

1 TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG GAGACGGTCA CAGCTTGTCT GTAAGCGGAT  
AGCGCGCAAA GCCACTACTG CCACTTTTGG AGACTGTGTA CGTCGAGGGC CTCTGCCAGT GTCGAACAGA CATTCGCCTA

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81 GCCGGGAGCA GACAAGCCCC TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG CGGCATCAGA  
CGGCCCTCGT CTGTTCCGGG AGTCCCGCGC AGTCGCCCAC AACC GCCCAC AGCCCCGACC GAATTGATAC GCCGTAGTCT

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161 GCAGATTGTA CTGAGAGTGC ACCATATGAA GCTTTTTGCA AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTAATTCTGG  
CGTCTAACAT GACTCTCACG TGGTATACTT CGAAAAACGT TTTCCGATCC GGAGGTTTTT TCGGAGGAGT GATGAAGACC

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241 AATAGCTCAG AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAT TAGTCAGCCA TGGGGCGGAG AATGGGCGGA  
TTATCGAGTC TCCGGCTCCG CCGGAGCCGG AGACGTATTT ATTTTTTTTA ATCAGTCGGT ACCCCGCCCTC TTACCCGCCCT

---

321 ACTGGGCGGG GAGGGAATTA TTGGCTATTG GCCATTGCAT ACGTTGTATC TATATCATAA TATGTACATT TATATTGGCT  
TGACCCGCC CTCCCTTAAT AACCGATAAC CGGTAACGTA TGCAACATAG ATATAGTATT ATACATGTAA ATATAACCGA

---

401 CATGTCCAAT ATGACCGCCA TGTGACATT GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT  
GTACAGGTTA TACTGGCGGT ACAACTGTAA CTAATAACTG ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA

---

481 AGCCCATATA TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC CCCGCCATT  
TCGGGTATAT ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC GGGTTGCTGG GGGCGGGTAA

---

561 GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT  
CTGCAGTTAT TACTGCATAC AAGGGTATCA TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

---

641 AAAGTGGCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTCCGCCC CCTATTGACG TCAATGACGG TAAATGGCCC  
TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCAGGCGGG GGATAACTGC AGTTACTGCC ATTTACCGGG

---

721 GCCTGGCATT ATGCCAGTA CATGACCTTA CGGGAATTTT CTAATTGGCA GTACATCTAC GTATTAGTCA TCGCTATTAC  
CGGACCGTAA TACGGGTCAT GTACTGGAAT GCCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT AGCGATAATG

---

801 CATGGTGATG CGGTTTTGGC AGTACACCAA TGGGCGTGGA TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA  
GTACCACTAC GCCAAAACCG TCATGTGGTT ACCCGCACCT ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT

---

881 TTGACGTCAA TGGGAGTTTG TTTTGGCACC AAAATCAACG GGAATTTTCCA AAATGTCGTA ATAACCCCGC CCCGTTGACG  
AACTGCAGTT ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT TATTGGGGCG GGGCAACTGC

---

961 CAAATGGGCG GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG  
GTTTACCCGC CATCCGCACA TGCCACCCCTC CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

---

1041 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC TCCGCGGCCG GGAACGGTGC ATTGGAACGC  
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTCGG AGGCGCGGGC CTTTGCCACG TAACCTTGCG

---

1121 GGATTCCCCG TGCCAAGAGT GACGTAAGTA CCGCCTATAG ACTCTATAGG CACACCCCTT TGGCTCTTAT GCATGCTATA  
CCTAAGGGGC ACGGTTCTCA CTGCATTCAT GCGGATATC TGAGATATCC GTGTGGGGAA ACCGAGAATA CGTACGATAT

---

1201 CTGTTTTTGG CTTGGGGCCT ATACACCCCC GCTCCTTATG CTATAGGTGA TGGTATAGCT TAGCCTATAG GTGTGGGTTA  
GACAAAAACC GAACCCCGGA TATGTGGGGG CGAGGAATAC GATATCCACT ACCATATCGA ATCGGATATC CACACCCAAT

---

1281 TTGACCATTA TTGACCACTC CCCTATTGGT GACGATACTT TCCATTACTA ATCCATAACA TGGCTCTTTG CCACAACAT  
AACTGGTAAT AACTGGTGAG GGGATAACCA CTGCTATGAA AGGTAATGAT TAGGTATTGT ACCGAGAAAC GGTGTTGATA

---

1361 CTCTATTGGC TATATGCCAA TACTCTGTCC TTCAGAGACT GACACGGACT CTGTATTTTT ACAGGATGGG GTCCATTTAT  
GAGATAACCG ATATACGGTT ATGAGACAGG AAGTCTCTGA CTGTGCCTGA GACATAAAAA TGTCCTACCC CAGGTAAATA

---

1441 TATTTACAAA TTCACATATA CAACAACGCC GTCCCCCGTG CCCGCAGTTT TTATTAAACA TAGCGTGGGA TCTCCGACAT  
ATAAATGTTT AAGTGTATAT GTTGTTCGG CAGGGGGCAC GGGCGTCAAA AATAATTTGT ATCGCACCTC AGAGGCTGTA

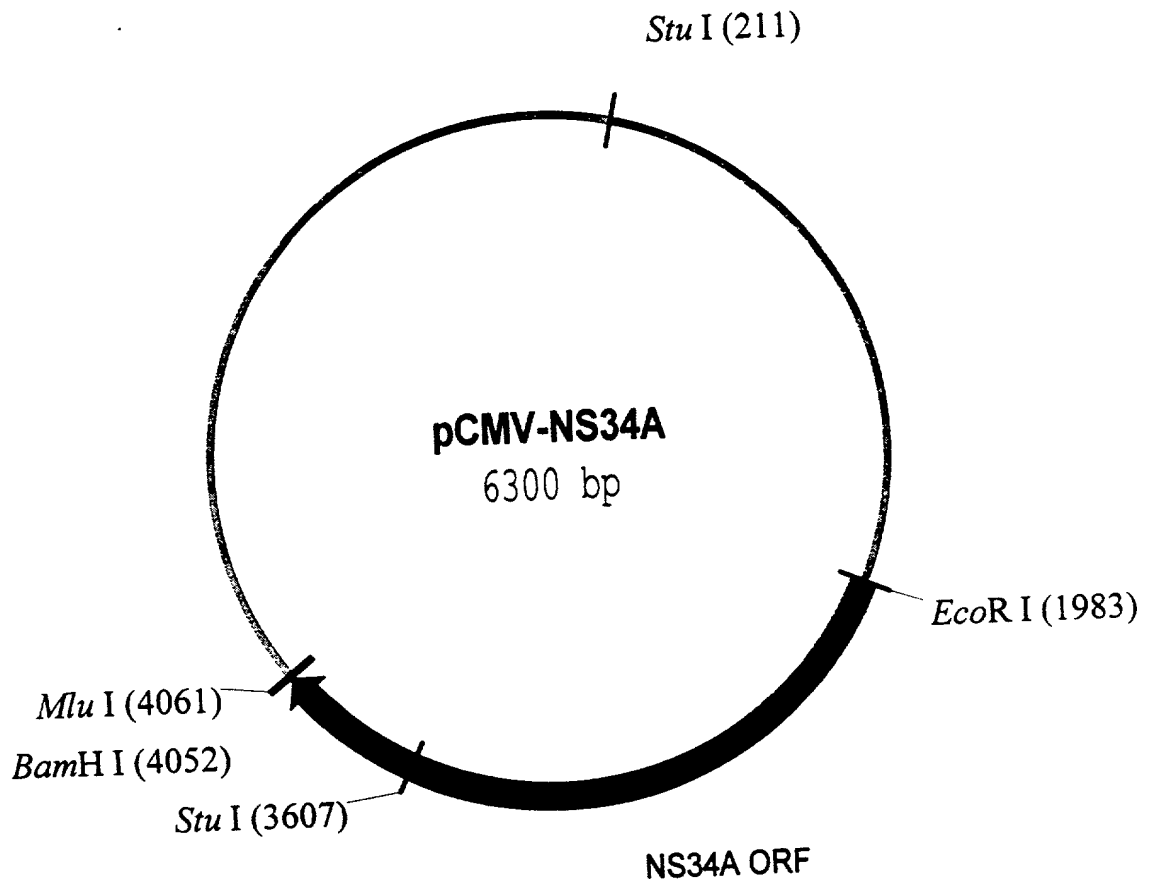
**FIGURE 7 - Page 2**

|      |                                           |                          |                                            |                                           |                          |                          |                                            |                          |
|------|-------------------------------------------|--------------------------|--------------------------------------------|-------------------------------------------|--------------------------|--------------------------|--------------------------------------------|--------------------------|
| 1521 | CTCGGGTACG<br>GAGCCCATGC                  | TGTTCCGGAC<br>ACAAGGCCTG | ATGGGCTCTT<br>TACCCGAGAA                   | CTCCGGTAGC<br>GAGGCCATCG                  | GGCGGAGCTT<br>CCGCCTCGAA | CCACATCCGA<br>GGTGTAGGCT | GCCCTGGTCC<br>CGGGACCAGG                   | CATCCGTCCT<br>GTAGGCAGGT |
| 1601 | GCGGCTCATG<br>CGCCGAGTAC                  | GTCGCTCGGC<br>CAGCGAGCCG | AGCTCCTTGC<br>TCGAGGAACG                   | TCCTAACAGT<br>AGGATTGTCA                  | GGAGGCCAGA<br>CCTCCGGTCT | CTTAGGCACA<br>GAATCCGTGT | GCACAATGCC<br>CGTGTTCACG                   | CACCACCACC<br>GTGGTGGTGG |
| 1681 | AGTGTGCCGC<br>TCACACGGCG                  | ACAAGGCCGT<br>TGTTCCGGCA | GGCGGTAGGG<br>CCGCCATCCC                   | TATGTGTCTG<br>ATACACAGAC                  | AAAATGAGCT<br>TTTTACTCGA | CGGAGATTGG<br>GCCTCTAACC | GCTCGCACCT<br>CGAGCGTGGG                   | GGACGCAGAT<br>CCTGCGTCTA |
| 1761 | GGAAGACTTA<br>CCTTCTGAAT                  | AGGCAGCGGC<br>TCCGTCGCGC | AGAAGAAGAT<br>TCTTCTTCTA                   | GCAGGCAGCT<br>CGTCCGTCGA                  | GAGTTGTTGT<br>CTCAACAACA | ATTCTGATAA<br>TAAGACTATT | GAGTCAGAGG<br>CTCAGTCTCC                   | TAACTCCCG<br>ATTGAGGGCA  |
| 1841 | TGCGGTGCTG<br>ACGCCACGAC                  | TTAACGGTGG<br>AATTGCCACC | AGGGCAGTGT<br>TCCCGTCACA                   | AGTCTGAGCA<br>TCAGACTCGT                  | GTA CTGCTG<br>CATGAGCAAC | CTGCCGCGCG<br>GACGGCGCGC | CGCCACCAGA<br>GCGGTGGTCT                   | CATAATAGCT<br>GTATTATCGA |
| 1921 | GACAGACTAA<br>CTGTCTGATT                  | CAGACTGTTC<br>GTCTGACAAG | CTTTCCATGG<br>GAAAGGTACC                   | GTCTTTTCTG<br>CAGAAAAGAC                  | CAGTCACCGT<br>GTCAGTGGCA | CGTCGACCTA<br>GCAGTGGAT  | EcoRI<br>~~~~~<br>AGAATTGAGA<br>TCTTAAGTCT | CTCGAGCAAG<br>GAGCTCGTTC |
| 2001 | XbaI<br>~~~~~<br>TCTAGAAAGG<br>AGATCTTTCC | CGCGCCAAGA<br>GCGCGGTTCT | BamHI<br>~~~~~<br>TATCAAGGAT<br>ATAGTTCCTA | MluI<br>~~~~~<br>CCACTACGCG<br>GGTGATGCGC | TTAGAGCTCG<br>AATCTCGAGC | CTGATCAGCC<br>GACTAGTCGG | TCGACTGTGC<br>AGCTGACACG                   | CTTCTAGTTG<br>GAAGATCAAC |
| 2081 | CCAGCCATCT<br>GGTCGGTAGA                  | GTTGTTTGCC<br>CAACAAACGG | CCTCCCCCGT<br>GGAGGGGGCA                   | GCCTTCCTTG<br>CGGAAGGAAC                  | ACCCTGGAAG<br>TGGGACCTTC | GTGCCACTCC<br>CACGGTGAGG | CACTGTCCTT<br>GTGACAGGAA                   | TCCTAATAAA<br>AGGATTATTT |
| 2161 | ATGAGGAAAT<br>TACTCCTTTA                  | TGCATCGCAT<br>ACGTAGCGTA | TGTCTGAGTA<br>ACAGACTCAT                   | GGTGTCAATC<br>CCACAGTAAG                  | TATTCTGGGG<br>ATAAGACCCC | GGTGGGGTGG<br>CCACCCACCC | GGCAGGACAG<br>CCGTCTGTGC                   | CAAGGGGGAG<br>GTTCCCCCTC |
| 2241 | GATTGGGAAG<br>CTAACCCCTT                  | ACAATAGCAG<br>TGTTATCGTC | GCATGCTGGG<br>CGTACGACCC                   | GAGTCTTTCC<br>CTCGAGAAGG                  | GCTTCCTCGC<br>CGAAGGAGCG | TCAGTACTCT<br>AGTGACTGAG | GCTGCGCTCG<br>CGACGCGAGC                   | GTCGTTCCGG<br>CAGCAAGCCG |
| 2321 | TGCGGCGAGC<br>ACGCCGCTCG                  | GGTATCAGCT<br>CCATAGTCGA | CACTCAAAGG<br>GTGAGTTTCC                   | CGGTAATACG<br>GCCATTATGC                  | GTTATCCACA<br>CAATAGGTGT | GAATCAGGGG<br>CTTAGTCCCC | ATAACGCAGG<br>TATTGCGTCC                   | AAAGAACATG<br>TTTCTGTGAC |
| 2401 | TGAGCAAAGG<br>ACTCGTTTTT                  | GCCAGCAAAA<br>CGGTGCTTTT | GGCCAGGAAC<br>CCGGTCTCTT                   | CGTAAAAAGG<br>GCATTTTTTC                  | CCGCGTTGCT<br>GGCGCAACGA | GGCGTTTTTC<br>CCGCAAAAAG | CATAGGCTCC<br>GTATCCGAGG                   | GCCCCCTGAG<br>CGGGGGGACT |
| 2481 | CGAGCATCAC<br>GCTCGTAGTG                  | AAAAATCGAC<br>TTTTTAGCTG | GCTCAAGTCA<br>CGAGTTCAGT                   | GAGGTGGCGA<br>CTCCACCGCT                  | AACCCGACAG<br>TTGGGCTGTC | GACTATAAAG<br>CTGATATTTT | ATACCAGGCG<br>TATGGTCCGC                   | TTTCCCCCTG<br>AAAGGGGGAC |
| 2561 | GAAGCTCCCT<br>CTTCGAGGGA                  | CGTGCGCTCT<br>GCACGCGAGA | CCTGTTCCGA<br>GGACAAGGCT                   | CCCTGCCGCT<br>GGGACGGCGA                  | TACCGGATAC<br>ATGGCCTATG | CTGTCCCGCT<br>GACAGGCGGA | TTCTCCCTTC<br>AAGAGGGAAG                   | GGAAGCGGTG<br>CCCTTCGCAC |
| 2641 | GCGCTTTCTC<br>CGCGAAAGAG                  | AATGCTCACG<br>TTACGAGTGC | CTGTAGGTAT<br>GACATCCATA                   | CTCAGTTCGG<br>GAGTCAAGCC                  | TGTAGGTCTG<br>ACATCCAGCA | TCGCTCCAAG<br>AGCGAGGTTC | CTGGGCTGTG<br>GACCCGACAC                   | TGCACGAACC<br>ACGTGCTTGG |
| 2721 | CCCCGTTTCG<br>GGGGCAAGTC                  | CCCGACCGCT<br>GGGCTGGCGA | GCGCCTTATC<br>CGCGGAATAG                   | CGGTAAGTAT<br>GCCATTGATA                  | CGTCTTGAGT<br>GCAGAACTCA | CCAACCCGGT<br>GGTTGGGCCA | AAGACACGAC<br>TTCTGTGCTG                   | TTATCGCCAG<br>AATAGCGGTG |
| 2801 | TGGCAGCAGC<br>ACCGTCGTCG                  | CACTGGTAAC<br>GTGACCATTG | AGGATTAGCA<br>TCCTAATCGT                   | GAGCGAGGTA<br>CTCGCTCCAT                  | TGTAGGCGGT<br>ACATCCGCCA | GCTACAGAGT<br>CGATGTCTCA | TCTTGAAGTG<br>AGAACTTCAC                   | GTGGCCTAAC<br>CACCAGGATT |
| 2881 | TACGGCTACA<br>ATGCCGATGT                  | CTAGAAGGAC<br>GATCTTCCTG | AGTATTTGGT<br>TCATAAACCA                   | ATCTGCGCTC<br>TAGACGCGAG                  | TGCTGAAGCC<br>ACGACTTCGG | AGTTACCTTC<br>TCAATGGAAG | GGAAAAAGAG<br>CCTTTTTCTC                   | TTGGTAGCTC<br>AACCATCGAG |

pCMV-II

|      |                          |                          |                          |                           |                           |                           |                           |                           |
|------|--------------------------|--------------------------|--------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| 2961 | TTGATCCGGC<br>AACTAGGCCG | AAACAAACCA<br>TTTGTTCGTT | CCGCTGGTAG<br>GGCGACCATC | CGGTGGTTTT<br>GCCACCAAAA  | TTTGTTCGCA<br>AAACAAACGT  | AGCAGCAGAT<br>TCGTCTGCTA  | TACGCGCAGA<br>ATGCGCGTCT  | AAAAAAGGAT<br>TTTTTTCCTA  |
| 3041 | CTCAAGAAGA<br>GAGTTCCTCT | TCCTTTGATC<br>AGGAAACTAG | TTTTCTACGG<br>AAAAGATGCC | GGTCTGACGC<br>CCAGACTGCG  | TCAGTGGAAC<br>AGTCACCTTG  | GAAAACCTAC<br>CTTTTGAGTG  | GTTAAGGGAT<br>CAATTCCCTA  | TTTGGTCATG<br>AAACCAAGTAC |
| 3121 | AGATTATCAA<br>TCTAATAGTT | AAAGGATCTT<br>TTTCCTAGAA | CACCTAGATC<br>GTGGATCTAG | CTTTTAAATT<br>GAAAATTTAA  | AAAAATGAAG<br>TTTTTACTTC  | TTTTAAATCA<br>AAAATTTAGT  | ATCTAAAGTA<br>TAGATTTTCAT | TATATGAGTA<br>ATATACTCAT  |
| 3201 | AACTTGGTCT<br>TTGAACCAGA | GACAGTTACC<br>CTGTCAATGG | AATGCTTAAT<br>TTACGAATTA | CAGTGAGGCA<br>GTCACCTCCG  | CCTATCTCAG<br>GGATAGAGTC  | CGATCTGTCT<br>GCTAGACAGA  | ATTTCTGTTCA<br>TAAAGCAAGT | TCCATAGTTG<br>AGGTATCAAC  |
| 3281 | CCTGACTCCC<br>GGACTGAGGG | CGTCGTGTAG<br>GCAGCACATC | ATAACTACGA<br>TATTGATGCT | TACGGGAGGG<br>ATGCCCTCCC  | CTTACCATCT<br>GAATGGTAGA  | GGCCCCAGTG<br>CCGGGGTCAC  | CTGCAATGAT<br>GACGTTACTA  | ACCGCGAGAC<br>TGGCGCTCTG  |
| 3361 | CCACGCTCAC<br>GGTGCGAGTG | CGGCTCCAGA<br>GCCGAGGTCT | TTTATCAGCA<br>AAATAGTCGT | ATAAACCAGC<br>TATTTGGTTCG | CAGCCGGAAG<br>GTCGGCCTTC  | GGCCGAGCGC<br>CCGGCTCGCG  | AGAAGTGGTC<br>TCTTCACCAG  | CTGCAACTTT<br>GACGTTGAAA  |
| 3441 | ATCCGCCTCC<br>TAGGCGGAGG | ATCCAGTCTA<br>TAGGTCAGAT | TTAATTGTTG<br>AATTAACAAC | CCGGGAAGCT<br>GGCCCTTCGA  | AGAGTAAGTA<br>TCTCATTCTA  | GTTCCGCCAGT<br>CAAGCGGTCA | TAATAGTTTG<br>ATTATCAAAC  | CGCAACGTTG<br>GCGTTGCAAC  |
| 3521 | TTGCCATTGC<br>AACGGTAACG | TACAGGCATC<br>ATGTCCGTAG | GTGGTGTCTC<br>CACCACAGTG | GCTCGTCGTT<br>CGAGCAGCAA  | TGGTATGGCT<br>ACCATACCGA  | TCATTTCAGCT<br>AGTAAGTCGA | CCGGTTCCCA<br>GGCCAAGGGT  | ACGATCAAGG<br>TGCTAGTTCC  |
| 3601 | CGAGTTACAT<br>GCTCAATGTA | GATCCCCCAT<br>CTAGGGGGTA | GTTGTGCAAA<br>CAACACGTTT | AAAGCGGTTA<br>TTTCGCCAAT  | GCTCCTTCGG<br>CGAGGAAGCC  | TCCTCCGATC<br>AGGAGGCTAG  | GTTGTGAGAA<br>CAACAGTCTT  | GTAAGTTGGC<br>CATTCAACCG  |
| 3681 | CGCAGTGTTA<br>GCGTCACAAT | TCACTCATGG<br>AGTGAGTACC | TTATGGCAGC<br>AATACCGTCG | ACTGCATAAT<br>TGACGTATTA  | TCTCTTACTG<br>AGAGAAATGAC | TCATGCCATC<br>AGTACGGTAG  | CGTAAGATGC<br>GCATTCTACG  | TTTTCTGTGA<br>AAAAGACACT  |
| 3761 | CTGGTGAGTA<br>GACCACTCAT | CTCAACCAAG<br>GAGTTGGTTC | TCATTCTGAG<br>AGTAAGACTC | AATAGTGTAT<br>TTATCACATA  | GCGGCGACCG<br>CGCCGCTGGC  | AGTTGCTCTT<br>TCAACGAGAA  | GCCC GGCGTC<br>CGGGCCGCAG | AATACGGGAT<br>TTATGCCCTA  |
| 3841 | AATACCGCGC<br>TTATGGCGCG | CACATAGCAG<br>GTGTATCGTC | AACTTTAAAA<br>TTGAAATTTT | GTGCTCATCA<br>CACGAGTAGT  | TTGGAAAACG<br>AACCTTTTGC  | TTCTTCGGGG<br>AAGAAGCCCC  | CGAAAACCTCT<br>GCTTTTGAGA | CAAGGATCTT<br>GTTCTTAGAA  |
| 3921 | ACCGCTGTTG<br>TGGCGACAAC | AGATCCAGTT<br>TCTAGGTCAA | CGATGTAACC<br>GCTACATTGG | CACTCGTGCA<br>GTGAGCACGT  | CCCAACTGAT<br>GGGTTGACTA  | CTTCAGCATC<br>GAAGTCGTAG  | TTTTACTTTC<br>AAAATGAAAG  | ACCAGCGTTT<br>TGGTCGCAAA  |
| 4001 | CTGGGTGAGC<br>GACCCACTCG | AAAAACAGGA<br>TTTTTGTCCT | AGGCAAAATG<br>TCCGTTTTAC | CCGCAAAAAA<br>GGCGTTTTTT  | GGGAATAAGG<br>CCCTTATTCC  | GCGACACGGA<br>CGCTGTGCCT  | AATGTTGAAT<br>TTACAACCTA  | ACTCATACTC<br>TGAGTATGAG  |
| 4081 | TTCTTTTTTC<br>AAGGAAAAAG | AATATTATTG<br>TTATAATAAC | AAGCATTTAT<br>TTCGTAAATA | CAGGGTTATT<br>GTCCCAATAA  | GTCTCATGAG<br>CAGAGTACTC  | CGGATACATA<br>GCCTATGTAT  | TTGAATGTA<br>AACTTACAT    | TTTAGAAAAA<br>AAATCTTTTT  |
| 4161 | TAAACAAATA<br>ATTTGTTTAT | GGGGTTCCGC<br>CCCCAAGGCG | GCACATTTCC<br>CGTGTAAGG  | CCGAAAAGTG<br>GGCTTTTCAC  | CCACCTGACG<br>GGTGGACTGC  | TCTAAGAAAC<br>AGATTCTTTG  | CATTATTATC<br>GTAATAATAG  | ATGACATTAA<br>TACTGTAATT  |
| 4241 | CCTATAAAAA<br>GGATATTTTT | TAGGCGTATC<br>ATCCGCATAG | ACGAGGCCCT<br>TGCTCCGGGA | TTCGTC<br>AAGCAG          |                           |                           |                           |                           |

FIGURE 8



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## FIGURE 9 - Page 1

1 TCGCGCGTTT CGGTGATGAC GGTGAAAACC TCTGACACAT GCAGCTCCCG  
AGCGCGCAAA GCCACTACTG CCACTTTTGG AGACTGTGTA CGTCGAGGGC

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51 GAGACGGTCA CAGCTTGTCT GTAAGCGGAT GCCGGGAGCA GACAAGCCCG  
CTCTGCCAGT GTCGAACAGA CATTGCGCTA CGGCCCTCGT CTGTTGCGGC

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101 TCAGGGCGCG TCAGCGGGTG TTGGCGGGTG TCGGGGCTGG CTTAACTATG  
AGTCCCGCGC AGTCGCCAC AACCGCCAC AGCCCGGACC GAATTGATAC

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151 CGGCATCAGA GCAGATTGTA CTGAGAGTGC ACCATATGAA GCTTTTGGCA  
GCCGTAGTCT CGTCTAACAT GACTCTCAG TGGTATACTT CGAAAAACGT

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StuI  
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201 AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG AATAGCTCAG
TTTCGGATCC GGAGGTTTTT TCGGAGGAGT GATGAAGACC TTATCGAGTC

251 AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAT TAGTCAGCCA
TCCGGCTCCG CCGGAGCCGG AGACGTATTT ATTTTTTTTA ATCAGTCGGT

301 TGGGGCGGAG AATGGGCGGA ACTGGGCGGG GAGGGAATTA TTGGCTATTG
ACCCCGCCTC TTACCCGCCT TGACCCGCC CTCCCTTAAT AACCGATAAC

351 GCCATTGCAT ACGTTGTATC TATATCATAA TATGTACATT TATATTGGCT
CGGTAACGTA TGCAACATAG ATATAGTATT ATACATGTAA ATATAACCGA

401 CATGTCCAAT ATGACCGCCA TGTGACATT GATTATTGAC TAGTTATTAA
GTACAGGTTA TACTGGCGGT ACAACTGTAA CTAATACTG ATCAATAATT

451 TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA TGGAGTTCCG
ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT ACCTCAAGGC

501 CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC
GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC GGGTTGCTGG

551 CCCGCCCAT GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA
GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA TTGCGGTTAT

601 GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT AACTGCCCCA
CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA TTTGACGGGT

651 CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTCCGCCC CCTATTGACG
GAACCGTCAT GTAGTTCACA TAGTATACGG TTCAGGCGGG GGATAACTGC

701 TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCAGTA CATGACCTTA
AGTTACTGCC ATTTACGGG CGGACCGTAA TACGGGTCAT GTACTGGAAT

751 CGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA TCGCTATTAC
GCCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT AGCGATAATG

801 CATGGTGATG CGGTTTTGGC AGTACACCAA TGGGCGTGGA TAGCGGTTTG
GTACCACTAC GCCAAAACCG TCATGTGGTT ACCCGCACCT ATCGCCAAAC

851 ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA TGGGAGTTTG
TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT ACCCTCAAAC

FIGURE 9 - Page 3

FIGURE 9 - Page 3

1851 TTAACGGTGG AG²GCA GTGT AGTCTGAGCA GTACTCGTTG CTGCCGCGCG
AATTGCCACC TCCCGTCACA TCAGACTCGT CATGAGCAAC GACGGCGCGC

1901 CGCCACCAGA CATAATAGCT GACAGACTAA CAGACTGTTC CTTTCCATGG
GCGGTGGTCT GTATTATCGA CTGTCTGATT GTCTGACAAG GAAAGGTACC

+2

M A P

ECORI

~ ~ ~ ~ ~

1951 GTCTTTTCTG CAGTCACCGT CGTCGACCTA AGAATTCACC ATGGCGCCCA
CAGAAAAGAC GTCAGTGGCA GCAGCTGGAT TCTTAAGTGG TACCGCGGGT

+2

+2 I T A Y A Q Q T R G L L G C I I T
 2001 TCACGGCGTA CGCCAGCAG ACAAGGGGCC TCCTAGGGTG CATAATCACC
 AGTGCCGCAT GCGGGTCGTC TGTTCCTCCG AGGATCCAC GTATTAGTGG

+2

+2 S L T G R D K N Q V E G E V Q I V
2051 AGCCTAACTG GCCGGGACAA AAACCAAGTG GAGGGTGAGG TCCAGATTGT
TCGGATTGAC CGGCCCTGTT TTTGGTTCAC CTCCCACTCC AGGTCTAACA

 $+2$

+2 S T A A Q T F L A T C I N G V C
 2101 GTCAACTGCT GCCCAAACCT TCCTGGCAAC GTGCATCAAT GGGGTGTGCT
 CAGTTGACGA CGGGTTTGA AGGACCGTTG CACGTAGTTA CCCCACACGA

+2

2151 +2 W T V Y H G A G T R T I A S P K G
 GGACTGTCTA CCACGGGGCC GGAACGAGGA CCATCGCGTC ACCCAAGGGT
 CCTGACAGAT GGTGCCCCGG CCTTGCTCTT GGTAGCGCAG TGGGTTCCCA

-2

-2 P V I Q M Y T N V D Q D L V G W P
 2201 CCTGTCATCC AGATGTATAC CAATGTAGAC CAAGACCTTG TGGGCTGGCC
 GGACAGTAGG TCTACATATG GTTACATCTG GTTCTGGAAC ACCCGACCGG

+2

+2 A S Q G T R S L T P C T C G S S
 2251 CGCTTCGCAA GGTACCCGCT CATTGACACC CTGCACTTGC GGCTCCTCGG
 GCGAAGCGTT CCATGGGCGA GTAAGTGTGG GACGTGAACG CCGAGGAGCC

+2

+2 D L Y L V T R H A D V I P V R R R
2301 ACCTTTACCT GGTCAAGAGG CACGCCGATG TCATTCCCGT GCGCCGGCGG
TGGAAATGGA CCAAGTCTCC GTGCGGCTAC AGTAAGGGCA CGCGGCCGCC

 $+2$

+2 G D S R G S L L S P R P I S Y L K
2351 GGTGATAGCA GGGGCAGCCT GCTGTCGCCC CGGCCCATTT CCTACTTGAA
CCACTATCGT CCCCCTCGGA CGACAGCGGG GCCCGGTAA GGATGAAC

 $+2$

+2 G S S G G P L L C P A G H A V G
 2401 AGGCTCCTCG GGGGTCCGC TGTGTGCC CGCGGGGCAC GCCGTGGGCA
 TCCGAGGAGC CCCCAGGCG ACAACACGGG GCGCCCCGTG CGGCACCCGT

+2

+2 I F R A A V C T R G V A K A V D F
2451 TATTTAGGGC CGCGGTGTGC ACCCGTGGAG TGGCTAAGGC GGTGGACTTT
ATAAAATCCCG GCGCCACACG TGGGCACCTC ACCGATTCCG CCACCTGAA

+2

+2 I P V E N L E T T M R S P V F T L
2501 ATCCCTGTGG AGAACCTAGA GACAACCATG AGGTCCCCGG TGTTACACGGA
TAGGGACACC TCTTGATCT CTGTTGGTAC TCCAGGGGCC ACAAGTGCCT

+2 S G D V V V V A T D A L M T G Y T
3201 GCGGCGATGT TGTCGTCGTG GCAACCGATG CCCTCATGAC CGGCTATACC
CGCCGCTACA ACAGCAGCAC CGTTGGCTAC GGGAGTACTG GCCGATATGG

Figure 1 consists of 12 line graphs arranged in a 4x3 grid. Each graph plots the percentage of total catch (Y-axis, 0 to 100) against time (X-axis, 1970 to 1990). The graphs are labeled 1 through 12, corresponding to different fish species. The fishing methods are indicated by the legend: 1. Gillnet, 2. Longline, and 3. Trawl. The species names are listed on the right side of the figure. The graphs show varying trends in catch percentages over the 20-year period.

Species	Method 1 (Gillnet)	Method 2 (Longline)	Method 3 (Trawl)
1. Yellowtail snapper	~80%	~10%	~10%
2. Black drum	~80%	~10%	~10%
3. Atlantic croaker	~80%	~10%	~10%
4. Gulf snapper	~80%	~10%	~10%
5. Gulf snapper	~80%	~10%	~10%
6. Gulf snapper	~80%	~10%	~10%
7. Gulf snapper	~80%	~10%	~10%
8. Gulf snapper	~80%	~10%	~10%
9. Gulf snapper	~80%	~10%	~10%
10. Gulf snapper	~80%	~10%	~10%
11. Gulf snapper	~80%	~10%	~10%
12. Gulf snapper	~80%	~10%	~10%

pCMV-NS34A

FIGURE 9 - Page 5

+2 G D F D S V I D C N T C V T Q T V
 3251 GCGACTTCG ACTCGGTGAT AGACTGCAAT ACGTGTGTCA CCCAGACAGT
 CCGCTGAAGC TGAGCCACTA TCTGACGTTA TGCACACAGT GGGTCTGTCA

+2 D F S L D P T F T I E T I T L P
 3301 CGATTTCAGC CTTGACCCTA CCTTCACCAT TGAGACAATC ACGCTCCCC
 GCTAAAGTCG GAACTGGGAT GGAAGTGGTA ACTCTGTTAG TGCGAGGGGG

+2 Q D A V S R T Q R R G R T G R G K
 3351 AAGATGCTGT CTCCCGCACT CAACGTCGGG GCAGGACTGG CAGGGGGAAG
 TTCTACGACA GAGGGCGTGA GTTGACGCCC CGTCTGACC GTCCCCCTTC

+2 P G I Y R F V A P G E R P S G M F
 3401 CCAGGCATCT ACAGATTTGT GGCACCGGGG GAGCGCCCCT CCGGCATGTT
 GGTCCGTAGA TGTCTAAACA CCGTGGCCCC CTCGCGGGGA GGCCGTACAA

+2 D S S V L C E C Y D A G C A W Y
 3451 CGACTCGTCC GTCCTCTGTG AGTGCTATGA CGCAGGCTGT GCTTGGTATG
 GCTGAGCAGG CAGGAGACAC TCACGATACT GCGTCCGACA CGAACCATAAC

+2 E L T P A E T T V R L R A Y M N T
 3501 AGCTCACGCC CGCCGAGACT ACAGTTAGGC TACGAGCGTA CATGAACACC
 TCGAGTGC GGCGCTCTGA TGTCAATCCG ATGCTCGCAT GTACTTGTGG

+2 P G L P V C Q D H L E F W E G V F
 3551 CCGGGGCTTC CCGTGTGCCA GGACCATCTT GAATTTTGGG AGGGCGTCTT
 GGCCCCGAAG GGCACACGGT CTTGGTAGAA CTTAAAACCC TCCCGCAGAA

+2 T G L T H I D A H F L S Q T K Q
 StuI
 ~~~~~  
 3601 TACAGGCCTC ACTCATATAG ATGCCCCACTT TCTATCCCAG ACAAAGCAGA  
 ATGTCCGGAG TGAGTATATC TACGGGTGAA AGATAGGGTC TGTTCGTCT

+2 S G E N L P Y L V A Y Q A T V C A  
 3651 GTGGGGAGAA CCTTCCTTAC CTGGTAGCGT ACCAAGCCAC CGTGTGCGCT  
 CACCCCTCTT GGAAGGAATG GACCATCGCA TGTTTCGGTG GCACACGCGA

+2 R A Q A P P P S W D Q M W K C L I  
 3701 AGGGCTCAAG CCCCTCCCC ATCGTGGGAC CAGATGTGGA AGTGTGTTGAT  
 TCCCGAGTTC GGGGAGGGGG TAGCACCTG GTCTACACCT TCACAACTA

+2 R L K P T L H G P T P L L Y R L  
 3751 TCGCCTCAAG CCCACCTCC ATGGGCCAAC ACCCTGCTA TACAGACTGG  
 AGCGGAGTTC GGGTGGGAGG TACCGGTTG TGGGGACGAT ATGTCTGACC

+2 G A V Q N E I T L T H P V T K Y I  
 3801 GCGCTGTTCA GAATGAAATC ACCCTGACGC ACCCAGTCAC CAAATACATC  
 CGCGACAAGT CTTACTTTAG TGGGACTGCG TGGGTCAGTG GTTTATGTAG

+2 M T C M S A D L E V V T S T W V L  
 3851 ATGACATGCA TGTCGGCCGA CCTGGAGGTC GTCACGAGCA CCTGGGTGCT  
 TACTGTACGT ACAGCCGGCT GGACCTCCAG CAGTGCTCGT GGACCCACGA

+2 V G G V L A A L A A Y C L S T G  
 3901 CGTTGGCGGC GTCCTGGCTG CTTTGGCCGC GTATTGCCTG TCAACAGGCT  
 GCAACCGCG CAGGACCGAC GAAACCGCG CATAACGGAC AGTTGTCCGA

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## FIGURE 9 - Page 6

+2 C V V I V G R V V L S G K P A I I  
 3951 GCGTGGTCAT AGTGGGCAGG GTCGTCTTGT CCGGGAAGCC GGCAATCATA  
 CGCACCAGTA TCACCCGTCC CAGCAGAACA GGCCCTTCGG CCGTTAGTAT

+2 P D R E V L Y R E F D E M E E C  
 4001 CCTGACAGGG AAGTCCTCTA CCGAGAGTTC GATGAGATGG AAGAGTGCTA  
 GGACTGTCCC TTCAGGAGAT GGCTCTCAAG CTA CTCTACC TTCTCAGAT

BamHI MluI  
 ~~~~~  
 4051 GGATCCACTA CGCGTTAGAG CTCGCTGATC AGCCTCGACT GTGCCTTCTA
 CCTAGGTGAT GCGCAATCTC GAGCGACTAG TCGGAGCTGA CACGGAAGAT

4101 GTTGCCAGCC ATCTGTTGTT TGCCCTCCC CCGTGCCTTC CTTGACCCTG
 CAACGGTCGG TAGACAACAA ACGGGGAGGG GGCACGGAAG GAACTGGGAC

4151 GAAGGTGCCA CTCCCCTGT CTTTCTCTAA TAAAATGAGG AAATTGCATC
 CTTCCACGGT GAGGGTGACA GGAAAGGATT ATTTTACTCC TTTAACGTAG

4201 GCATTGTCTG AGTAGGTGTC ATTCTATTCT GGGGGGTGGG GTGGGGCAGG
 CGTAACAGAC TCATCCACAG TAAGATAAGA CCCCCACCC CACCCCGTCC

4251 ACAGCAAGGG GGAGGATTGG GAAGACAATA GCAGGCATGC TGGGGAGCTC
 TGTCGTTCCC CCTCCTAACC CTTCTGTTAT CGTCCGTACG ACCCCTCGAG

4301 TTCCGCTTCC TCGCTCACTG ACTCGCTGCG CTCGGTCGTT CGGCTGCGGC
 AAGGCGAAGG AGCGAGTGAC TGAGCGACGC GAGCCAGCAA GCCGACGCCG

4351 GAGCGGTATC AGCTCACTCA AAGGCGGTAA TACGTTATC CACAGAATCA
 CTCGCCATAG TCGAGTGAGT TTCCGCCATT ATGCCAATAG GTGTCTTAGT

4401 GGGGATAACG CAGGAAAGAA CATGTGAGCA AAAGGCCAGC AAAAGGCCAG
 CCCCTATTGC GTCCTTCTTT GTACTCTCGT TTTCCGGTCG TTTTCCGGTC

4451 GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG CTCCGCCCCC
 CTTGGCATT TTCCGGCGCA ACGACCGCAA AAAGGTATCC GAGGCGGGGG

4501 CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCCG
 GACTGCTCGT AGTGTTTTGA GCTGCGAGTT CAGTCTCCAC CGCTTTGGGC

4551 ACAGGACTAT AAAGATACCA GCGGTTTCCC CCTGGAAGCT CCCTCGTGCG
 TGTCCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA GGGAGCACGC

4601 CTCTCCTGTT CCGACCCTGC CGCTTACCGG ATACCTGTCC GCCTTTCTCC
 GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG CGGAAAGAGG

4651 CTTGCGGAAG CGTGGCGCTT TCTCAATGCT CACGCTGTAG GTATCTCAGT
 GAAGCCCTTC GCACCGCGAA AGAGTTACGA GTGCGACATC CATAGAGTCA

4701 TCGGTGTAGG TCGTTGCTC CAAGCTGGGC TGTGTGCACG AACCCCCCGT
 AGCCACATCC AGCAAGCGAG GTTCGACCCG ACACACGTGC TTGGGGGGCA

4751 TCAGCCCGAC CGCTGCGCCT TATCCGGTAA CTATCGTCTT GAGTCCAACC
 AGTCGGGCTG GCGACGCGGA ATAGGCCATT GATAGCAGAA CTCAGGTTGG

4801 CGGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT
 GCCATTCTGT GCTGAATAGC GGTGACCGTC GTCGGTGACC ATTGTCTTAA

FIGURE 9 - Page 7

4851 AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA AGTGGTGGCC
TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAACT TCACCACCGG

4901 TAACTACGGC TACACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA
ATTGATGCCG ATGTGATCTT CCTGTCATAA ACCATAGACG CGAGACGACT

4951 AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAAACA
TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAACTAG GCCGTTTGTT

5001 ACCACCGCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGCG
TGGTGGCGAC CATCGCCACC AAAAAAACA ACGTTTCGTCG TCTAATGCGC

5051 CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT ACGGGGTCTG
GTCTTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAGA TGCCCCAGAC

5101 ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA
TGCGAGTCAC CTTGCTTTTG AGTGCAATTC CCTAAAACCA GTACTCTAAT

5151 TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATTAAAAAT GAAGTTTAA
AGTTTTTCCT AGAAGTGGAT CTAGGAAAAT TTAATTTTTA CTTCAAAATT

5201 ATCAATCTAA AGTATATATG AGTAACTTG GTCTGACAGT TACCAATGCT
TAGTTAGATT TCATATATAC TCATTGAAC CAGACTGTCA ATGGTTACGA

5251 TAATCAGTGA GGCACCTATC TCAGCGATCT GTCTATTTTCG TTCATCCATA
ATTAGTCACT CCGTGGATAG AGTCGCTAGA CAGATAAAGC AAGTAGGTAT

5301 GTTGCCCTGAC TCCCCGTCGT GTAGATAACT ACGATACGGG AGGGCTTACC
CAACGGACTG AGGGGCAGCA CATCTATTGA TGCTATGCCC TCCCGAATGG

5351 ATCTGCCCCC AGTGCTGCAA TGATACCGCG AGACCCACGC TCACCGGCTC
TAGACCGGGG TCACGACGTT ACTATGGCGC TCTGGGTGCG AGTGCCGAG

5401 CAGATTTATC AGCAATAAAC CAGCCAGCCG GAAGGGCCGA GCGCAGAAGT
GTCTAAATAG TCGTTATTTG GTCGGTCGGC CTTCCCGGCT CGCGTCTTCA

5451 GGTCTGCAA CTTTATCCGC CTCCATCCAG TCTATTAATT GTTGCCGGGA
CCAGGACGTT GAAATAGGCG GAGGTAGGTC AGATAATTAA CAACGGCCCT

5501 AGCTAGAGTA AGTAGTTCGC CAGTTAATAG TTTGCGCAAC GTTGTTGCCA
TCGATCTCAT TCATCAAGCG GTCAATTATC AAACGCGTTG CAACAACGGT

5551 TTGCTACAGG CATCGTGGTG TCACGCTCGT CGTTTGGTAT GGCTTCATT
AACGATGTCC GTAGCACCAC AGTGCAGCA GCAAACCATA CCGAAGTAAG

5601 AGCTCCGGTT CCCAACGATC AAGGCGAGTT ACATGATCCC CCATGTTGTG
TCGAGGCCAA GGGTTGCTAG TTCCGCTCAA TGTACTAGGG GGTACAACAC

5651 CAAAAAGCG GTTAGCTCCT TCGGTCCTCC GATCGTTGTC AGAAGTAAGT
GTTTTTTCGC CAATCGAGGA AGCCAGGAGG CTAGCAACAG TCTTCATTCA

5701 TGGCCGCGAGT GTTATCACTC ATGGTTATGG CAGCACTGCA TAATTCTCTT
ACCGGCGTCA CAATAGTGAG TACCAATACC GTCGTGACGT ATTAAGAGAA

5751 ACTGTCATGC CATCCGTAAG ATGCTTTTCT GTGACTGGTG AGTACTCAAC
TGACAGTACG GTAGGCATTC TACGAAAAGA CACTGACCAC TCATGAGTTG

FIGURE 9 - Page 8

5801	CAAGTCATTC GTTCAAGTAAG	TGAGAATAGT ACTCTTATCA	GTATGCGGCG CATACGCCGC	ACCGAGTTGC TGGCTCAACG	TCTTGCCCGG AGAACGGGCC
5851	CGTCAATACG GCAGTTATGC	GGATAATACC CCTATTATGG	GCGCCACATA CGCGGTGTAT	GCAGAACTTT CGTCTTGAAA	AAAAGTGCTC TTTTACAGAG
5901	ATCATTGGAA TAGTAACCTT	AACGTTCTTC TTGCAAGAAG	GGGGCGAAAA CCCCGCTTTT	CTCTCAAGGA GAGAGTTCCCT	TCTTACCGCT AGAATGGCGA
5951	GTTGAGATCC CAACTCTAGG	AGTTCGATGT TCAAGCTACA	AACCCACTCG TTGGGTGAGC	TGCACCCAAC ACGTGGGTTG	TGATCTTCAG ACTAGAAGTC
6001	CATCTTTTAC GTAGAAAATG	TTTCACCAGC AAAGTGGTCG	GTTTCTGGGT CAAAGACCCA	GAGCAAAAAC CTCGTTTTTG	AGGAAGGCAA TCCTTCCGTT
6051	AATGCCGCAA TTACGGCGTT	AAAAGGGAAT TTTTCCCTTA	AAGGGCGACA TTCCCGCTGT	CGGAAATGTT GCCTTTACAA	GAATACTCAT CTTATGAGTA
6101	ACTCTTCCCT TGAGAAGGAA	TTTCAATATT AAAGTTATAA	ATTGAAGCAT TAACTTCGTA	TTATCAGGGT AATAGTCCCA	TATTGTCTCA ATAACAGAGT
6151	TGAGCGGATA ACTCGCCTAT	CATATTTGAA GTATAAACTT	TGTATTTAGA ACATAAATCT	AAAATAAACA TTTTATTTGT	AATAGGGGTT TTATCCCCAA
6201	CGCGGCACAT GGCGCGTGTA	TTCCCCGAAA AAGGGGCTTT	AGTGCCACCT TCACGGTGGA	GACGTCTAAG CTGCAGATTG	AAACCATTAT TTTGGAATAA
6251	TATCATGACA ATAGTACTGT	TTAACCTATA AATTGGATAT	AAAATAGGCG TTTTATCCGC	TATCACGAGG ATAGTGCTCC	CCCTTTCGTC GGGAAAGCAG

[illegible]

Diagram 1

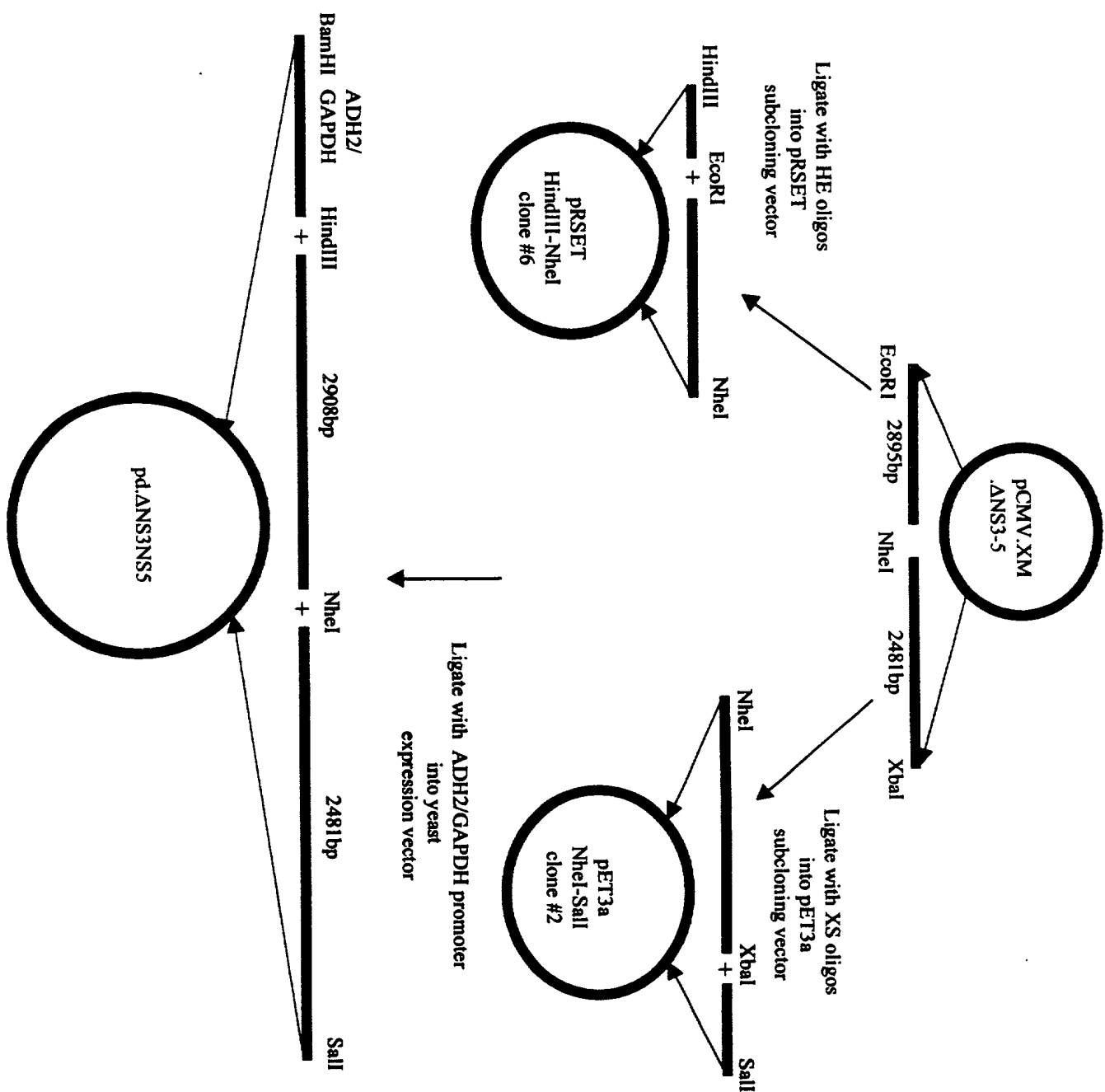


FIGURE 11 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuVal
 2 AGCTTACAAAACAAATTCACCATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTA
 TCGAATGTTTTGTTAAGTGGTACCGACGTATACGTCGAGTCCCGATATTCCACGATCAT
 ^ ^ ^ ^
 1 HIND3, 21 NCOI, 30 NDEI, 58 SCAI,

LeuAsnProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGly
 62 CTCAACCCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGG
 GAGTTGGGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCC

IleAspProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyr
 122 ATCGATCCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTAC
 TAGCTAGGATTGTAGTCTTGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATG
 ^
 122 CLAI,

SerThrTyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIle
 182 TCCACCTACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATA
 AGGTGGATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTAT

IleCysAspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeu
 242 ATTTGTGACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGCCTT
 TAAACACTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAA

AspGlnAlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGly
 302 GACCAAGCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGC
 CTGGTTTCGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCC
 ^
 309 ALWN1,

SerValThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIle
 362 TCCGTCACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATC
 AGGCAGTGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAG

ProPheTyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePhe
 422 CCTTTTTACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTC
 GGAAAAATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAG

CysHisSerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsn
 482 TGTCATTCAAAGAAGAAGTGCGACGAACCTGCCGCAAAGCTGGTCGCATTGGGCATCAAT
 ACAGTAAGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTA

AlaValAlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValVal
 542 GCCGTGGCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCGACCAGCGGCGATGTTGTC
 CGGCACCGGATGATGGCGCCAGAAGTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAG
 ^ ^
 556 SAC2, 566 DRD1,

ValValAlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAsp
 602 GTCGTGGCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGAC
 CAGCACCGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTG
 ^
 621 BSPH1,

CysAsnThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGlu

00244530

[illegible]

662 TGCAATACGTGTGTACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTGAG
ACGTTATGCACACAGTGGGTCTGTCTCAGCTAAAGTCGGAACCTGGGATGGAAGTGGTAACTC

722 ThrIleThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArg
ACAATCACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGG
TGTTAGTGCAGGGGGTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCTTGACCGTCC

782 GlyLysProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAsp
GGGAAGCCAGGCATCTACAGATTTGTGGCACCGGGGAGCGCCCCCTCCGGCATGTTTCGAC
CCCTTCGGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGGCCGTACAAGCTG

822 BGLI, 839 DRD1,

842 SerSerValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAla
TCGTCCGTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCGCC
AGCAGGCAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGG

887 SACI,

902 GluThrThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAsp
GAGACTACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGAC
CTCTGATGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTTG

937 SMAI XMAI,

962 HisLeuGluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeu
CATCTTGAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTTCTA
GTAGAACTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGAT

991 STUI,

1022 SerGlnThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrVal
TCCCAGACAAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTG
AGGGTCTGTTTCGTCTCACCCCTCTTGGGAAGGAATGGACCATCGCATGGTTCGGTGGCAC

1075 DRA3,

1082 CysAlaArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArg
TGCGCTAGGGCTCAAGCCCTCCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCG
ACGCGATCCCAGTTCGGGGAGGGGGTAGCACCTGGTCTACACCTTACAACTAAGCG

1142 LeuLysProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsn
CTCAAGCCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTGAGAAT
GAGTTCGGGTGGGACTACCCGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTA

1156 NCOI,

1202 GluIleThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeu
GAAATCACCTGACGCACCCAGTACCAAATACATCATGACATGCATGTGGCCGACCTG
CTTTAGTGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGAC

1236 BSPH1, 1240 DRD1, 1243 AVA3, 1251 EAG1 XMA3, 1256 DRD1,

1262 GluValValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyr
GAGGTCGTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCTGGTGCTTTGGCCGCGTAT
CTCCAGCAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATA

FIGURE 11 - Page 3

CysLeuSerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAla
 1322 TGCCTGTCAACAGGCTGCGTGGTCATAGTGGGCAGGGTTCGTCTTGTCCGGGAAGCCGGCA
 ACGGACAGTTGTCCGACGCACCAAGTATCACCCGTCAGCAGAACAGGCCCTTCGGCCGT
 1375 NAEI,
 IleIleProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGln
 1382 ATCATACCTGACAGGGAAGTCCTCTACCGAGAGTTTCGATGAGATGGAAGAGTGCTCTCAG
 TAGTATGGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCACGAGAGTC
 1391 DRD1,
 HisLeuProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeu
 1442 CACTTACCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTC
 GTGAATGGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAG
 GlyLeuLeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsn
 1502 GGCCTCCTGCAGACCGCGTCCCGTCAGGCAGAGTTATCGCCCCTGCTGTCCAGACCAAC
 CCGGAGGACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTG
 1508 PSTI, 1513 TTH3I,
 TrpGlnLysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGln
 1562 TGGCAAAACTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAA
 ACCGTTTTTGTAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCTATGTT
 1571 XHOI, 1592 NDEI,
 TyrLeuAlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPhe
 1622 TACTTGGCGGGCTTGTCAACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTT
 ATGAACCGCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAACACCGAAAA
 1649 BSTE2,
 ThrAlaAlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGly
 1682 ACAGCTGCTGTCACCAAGCCACTAACCCTAGCCAAACCCCTCTTCAACATATTGGGG
 TGTCGACGACAGTGGTCCGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCC
 1683 ALWN1 PVU2,
 GlyTrpValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGly
 1742 GGGTGGGTGGCTGCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGC
 CCCACCCACCGACGGTTCGAGCGGGGGGCCACGGCGATGACGGAAACACCCGCGACCG
 1800 ESP1,
 LeuAlaGlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAla
 1802 TTAGCTGGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCA
 AATCGACCGCGGCGGTAGCCGTCAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGT
 1808 KAS1 NARI,
 GlyTyrGlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluVal
 1862 GGGTATGGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTC
 CCCATACCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAG

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[illegible]

ProSerThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuVal
1922 CCCTCCACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTA
GGGAGGTGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCAT
1934 TTH3I,
ValGlyValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaVal
1982 GTCGGCGTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGGCGAGGGGGCAGTG
CAGCCGCACCAGACAGTCGTTATGACGCGGGCGTGCAACCGGGCCCGCTCCCCCGTCAC
2010 NAEI, 2023 SMAI XMAI,
GlnTrpMetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHis
2042 CAGTGGATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCCACGCAC
GTCACCTACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGTGCGTG
2073 SMAI XMAI, 2099 DRA3,
TyrValProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrVal
2102 TACGTGCCGGAGAGCGATGCAGCTGCCCCGCTCACTGCCATACTCAGCAGCCTCACTGTA
ATGCACGGCCTCTCGCTACGTGACGGGCGCAGTGACGGTATGAGTCGTGCGAGTGACAT
2121 PVU2,
ThrGlnLeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSer
2162 ACCCAGCTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTACCACTCCATGCTCC
TGGGTCGAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGG
2165 ALWN1, 2170 MST2,
GlySerTrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThr
2222 GGTTCCTGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACC
CCAAGGACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACTCGCTGAAATTCTGG
2226 ECON1,
TrpLeuLysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArg
2282 TGGCTAAAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCTGCCAGCGC
ACCGATTTTCGATTGAGTACGGTGTGACGCGACCCTAGGGGAAACACAGGACGGTTCGGC
2291 ESP1, 2306 PVU2, 2316 BAMHI,
GlyTyrLysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAla
2342 GGGTATAAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCT
CCCATATTCCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGA
2402 GluIleThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArg
GAGATCACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCTAGGACCTGCAGG
CTCTAGTGACCTGTACAGTTTTTGCCCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCC
2431 BSAB1, 2447 AVR2, 2454 SSE83871, 2455 PSTI,
AsnMetTrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeu
2462 AACATGTGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCGTACCCCCCTT
TTGTACACCTCACCTGGAAGGGGTAATTACGGATGTGGTGGCCGGGGACATGGGGGGAA

3102 BGL2,

FIGURE 11 - Page 6

IleLeuArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyr
 3122 ATCCTGCGGAAGTCTCGGAGATTCGCCCAGGCCCTGCCCGTTTGGGCGCGGCCGACTAT
 TAGGACGCCCTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCTGATA
 ^ ^
 3149 ALWN1, 3170 EAG1 XMA3,

 AsnProProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGly
 3182 AACCCCCCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGC
 TTGGGGGGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCG
 ^ ^
 3223 HGIE2, 3235 NCOI,

 CysProLeuProProProLysSerProProValProProProArgLysLysArgThrVal
 3242 TGCCCGCTTCCACCTCCAAAGTCCCCCTCCTGTGCCTCCGCCTCGGAAGAAGCGGACGGTG
 ACGGGCGAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCAC

 ValLeuThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGly
 3302 GTCCTCACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGC
 CAGGAGTGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCG
 ^ ^
 3338 SACI, 3352 HIND3,

 SerSerSerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaPro
 3362 AGCTCCTCAACTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCT
 TCGAGGAGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGA

 SerGlyCysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGly
 3422 TCTGGCTGCCCCCGGACTCCGACGTGAGTCCTATTCTCCATGCCCCCTGGAGGGG
 AGACCGACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGACCTCCCC
 ^
 3443 EAM11051,

 GluProGlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsn
 3482 GAGCCTGGGGATCCGGATCTTAGCGACGGGTCATGGTCAACGGTCAGTAGTGAGCCAAC
 CTCGGACCCCTAGGCCTAGAATCGCTGCCCAGTACCAGTTGCCAGTCATCACTCCGGTTG
 ^ ^ ^
 3490 BAMHI, 3491 BSAB1, 3493 BSPE1,

 AlaGluAspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrPro
 3542 GCGGAGGATGTCTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCG
 CGCCTCCTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGC
 ^
 3595 DRA3,

 CysAlaAlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHis
 3602 TGCGCCGCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTAC
 ACGCGGCGCCTTCTGTCTTTGACGGGTAGTTACGTGATTCTGTTGAGCAACGATGCAGTG
 ^ ^ ^
 3606 SAC2, 3617 ALWN1, 3661 PFLM1,

 HisAsnLeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThr
 3662 CACAATTTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAGAAAGTCACA
 GTGTTAAACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTAGTGT
 ^
 3687 DRA3,

 PheAspArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAla

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3722 TTTGACAGACTGCAAGTTCTTGGACAGCCATTACCAGGACGGTACTCAAGGAGGTTAAAGCA
AAACTGTCTGACGTTCAAGACCTGTGCGTAATGGTCCTGCATGAGTTCCTCCAATTCGT

AlaAlaSerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrPro
3782 GCGGCGTCAAAAGTGAAGGCTAAGTTCGCTATCCGTAGAGGAAGCTTGCAGCCTGACGCC
CGCCGAGTTTTTCACTTCGGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGG
^

3822 HIND3,

ProHisSerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArg
3842 CCACACTCAGCCAAATCCAAGTTTGGTTATGGGGCAAAAGACGTCCGTTGCCATGCCAGA
GGTGTGAGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGTCAGGCAACGGTACGGTCT
^ ^

3881.AAT2, 3896 BGLI,

LysAlaValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrPro
3902 AAGGCCGTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCA
TTCCGGCATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGT

IleAspThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGly
3962 ATAGACACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTCAGCCTGAGAAGGGGGGT
TATCTGTGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGACTCTTCCCCCA

ArgLysProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMet
4022 CGTAAGCCAGCTCGTCTCATCGTGTCCCCGATCTGGGCGTGC GCGTGTGCGAAAAGATG
GCATTCCGTCGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTAC

AlaLeuTyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPhe
4082 GCTTTGTACGACGTGGTTACAAAGCTCCCCTTGGCCGTGATGGGAAGCTCCTACGGATT
CGAAACATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCTTCGAGGATGCCTAAG

GlnTyrSerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThr
4142 CAATACTCACCAGGACAGCGGTTGAATTCCTCGTGCAAGCGTGAAGTCCAAGAAAACC
GTTATGAGTGGTCCTGTCGCCCACTTAAGGAGCACGTTGCGACCTTCAGGTTCTTTTGG
^

4166 ECOR1,

ProMetGlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIle
4202 CCAATGGGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATC
GGTTACCCCAAGAGCATACTATGGGCGACGAAACTGAGGTGTCAGTGACTCTCGCTGTAG
^ ^

4235 DRD1, 4242 ALWN1,

ArgThrGluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIle
4262 CGTACGGAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCCAAGCCCGCTGGCCATC
GCATGCCTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTTCGGGGCGACCGGTAG
^ ^

4307 BGLI, 4314 BALI,

LysSerLeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsn
4322 AAGTCCCTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAAC
TTCAGGGAGTGGCTCTCCGAAATACAACCCCGGGGAGAATGGTTAAGTCCCCCTCTTG
^

4351 APAI,

CysGlyTyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeu
4382 TGCGGCTATCGCAGGTGCCGCGGAGCGGCGTACTGACAACCTAGCTGTGGTAACACCTC

[illegible]

ACGCCGATAGCGTCCACGGCGCGCTCGCCGATGACTGTTGATCGACACCATTTGTGGGAG

4442 ThrCysTyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMet
ACTTGCTACATCAAGGCCCCGGGCAGCCTGTCTGAGCCGAGGGCTCCAGGACTGCACCATG
TGAACGATGTAGTTCCGGGCCCCGTCTGGACAGCTCGGCGTCCCAGGTCCTGACGTGGTAC

4458 SMAI XMAI,

4502 LeuValCysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAla
CTCGTGTGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCG
GAGCACACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCCTCTCGCG

4514 DRD1, 4517 TTH3I,

4562 AlaSerLeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspPro
GCGAGCCTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCC
CGCTCGGACTCTCGGAAGTGCTCCGATACTGGTCCATGAGGCGGGGGGGACCCCTGGGG

4622 ProGlnProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAla
CCACAACCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTCTAGTCGCC
GGTGTGGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGG

4643 SACI,

4682 HisAspGlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAla
CACGACGGCGCTGGAAAGAGGGTCTACTACCTCACCCGTGACCTACAACCCCCCTCGCG
GTGCTGCCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGC

4737 NRUI,

4742 ArgAlaAlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIle
AGAGCTGCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATC
TCTCGACGCACCTCTGTCGTTCTGTGTGAGGTCAAGTAAAGACCGATCCGTTGTATTAG

4802 MetPheAlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeu
ATGTTTGGCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTCTTTAGCGTCTCT
TACAAACGGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAA

4812 PFLM1, 4813 DRA3,

4862 IleAlaArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSer
ATAGCCAGGGACAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCC
TATCGGTCCCTGGTCAACTTGTCCGGGAGCTAACGCTCTAGATGCCCCGACGATGAGG

4899 BGL2,

4922 IleGluProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSer
ATAGAACCCTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCA
TATCTTGGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAGT

4960 NCOI,

4982 LeuHisSerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGly
CTCCACAGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGATGCCTCAGAAAACCTTGGG
GAGGTGTCAATGAGAGGTCCTCTTAGTTATCCACCGCGTACGGAGTCTTTTGAACCC

5021 SPHI, 5041 KPNI,

[illegible]

ValProProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAla
5042 GTACCGCCCTTGCGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCC
CATGGCGGGAACGCTCGAACCTCTGTGGCCCGGGCCTCGCAGGCGCGATCCGAAGACCGG
5070 APAI, 5097 BALI,
ArgGlyGlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLys
5102 AGAGGAGGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAG
TCTCCTCCGTCCCACGGTATACACCGTTTCATGGAGAAGTTGACCCGTCATTCTTGTTC
5119 NDEI,
LeuLysLeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAla
5162 CTCAAACCTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCT
GAGTTTGAGTGAGGTTATCGCCGGCGACCGGTCGACCTGAACAGGCCGACCAAGTGCCGA
5180 NOTI, 5181 EAG1 XMA3, 5188 BALI, 5192 PVU2,
GlyTyrSerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrp
5222 GGCTACAGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGGCCCCGCTGGATCTGG
CCGATGTCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCGGGGGCGACCTAGACC
5246 DRA3,
PheCysLeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgOP
5282 TTTTGCCTACTCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGATGAAGG
AAAACGGATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTACTTCC
5301 PSTI, 5331 HGIE2,
TTGGGGTAACACTCCGGCCTAAAAAAAAAAAAAAAAATCTAGAACCCGAGTCGAC
5342 AACCCCATTTGTGAGGCCGATTTTTTTTTTTTTTTTAGATCTTGGGCTCAGCTG
5378 XBAI, 5390 SALI,

FIGURE 12

~~NO~~
 6B
 std

PAS
 C

C.1 C.2

KD_{cr}

250 -

98 -

64 -

50 -

36 -

30 -

16 -

6 -

4 -

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FIGURE 13

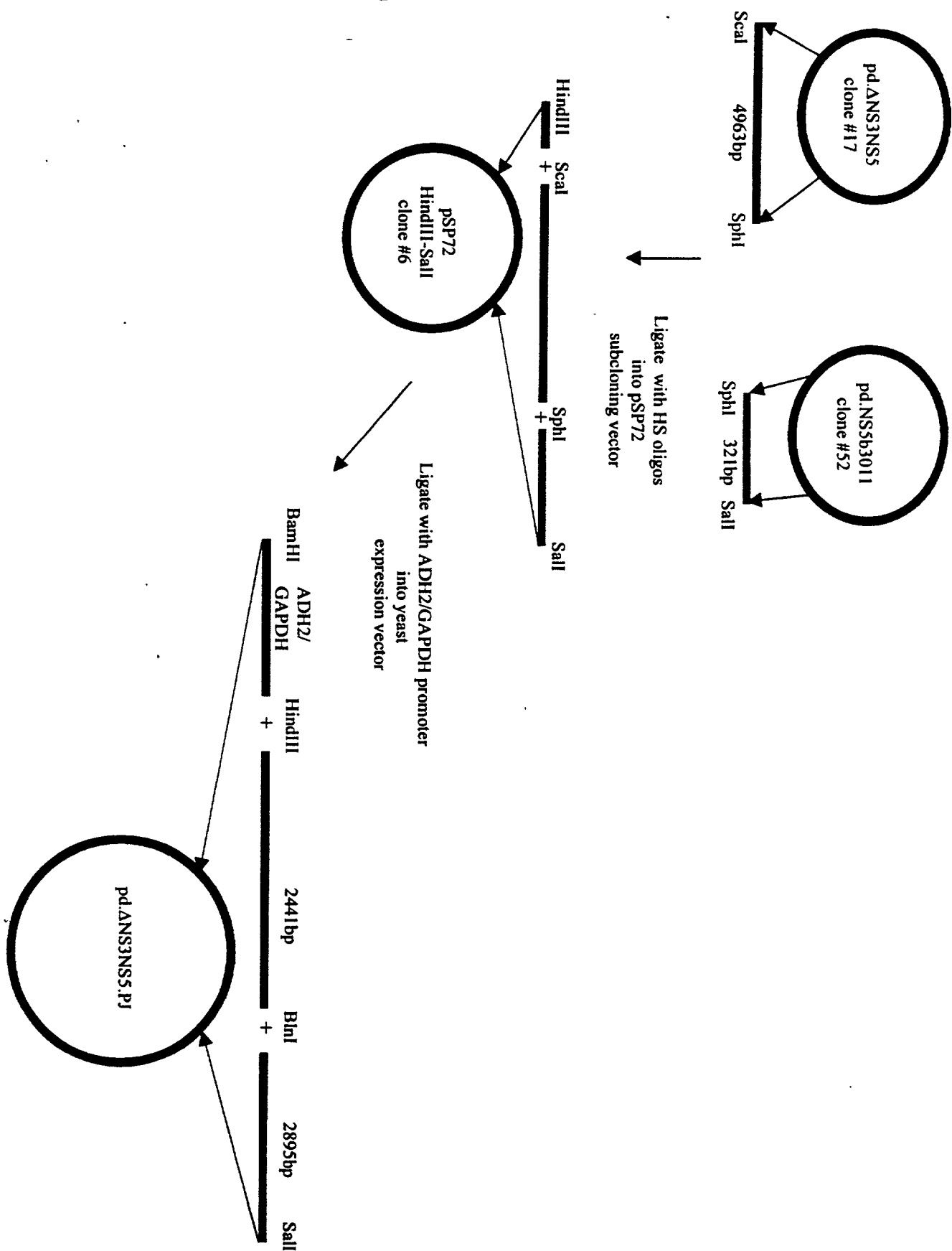


FIGURE 14 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn
 2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC
 TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG
 ^ ^ ^
 1 HIND3, 24 NDEI, 52 SCAI,
 ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp
 62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT
 GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA
 ^
 116 CLAI,
 ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr
 122 CCTAACATCAGGACCGGGTGAGAACAATTACCACTGGCAGCCCCATCAGTACTCCACC
 GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGATGAGGTGG
 TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys
 182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT
 ATGCCGTTCAAGGAACGGCTGCCGCCCCACGAGCCCCCGCAATACTGTATTATTAAACA
 AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln
 242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA
 CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT
 AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal
 302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC
 CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG
 ^
 303 ALWN1,
 ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe
 362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGAGAGATCCCTTTT
 TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA
 TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis
 422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT
 ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA
 SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal
 482 TCAAAGAAGAAGTGCGACGAACCTGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG
 AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal
 542 GCCTACTACCGGGTCTTGACGTGTCCGTCATCCCGACCAGCGCGATGTTGTGTCGTCGTG
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCGCTACAACAGCAGCAC
 ^ ^
 550 SAC2, 560 DRD1,
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA
 ^
 615 BSPH1,
 ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle

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662 ACGTGTGTCACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTGAGACAATC
TGCACACAGTGGGTCTGTCTAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACTCTGTTAG

722 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys
ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGGAAG
TGCAGAGGGGTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCCCCCTTC

782 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer
CCAGGCATCTACAGATTTGTGGCACCAGGGGAGCGCCCCCTCCGGCATGTTGACTCGTCC
GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG

816 BGLI, 833 DRD1,

842 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr
GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGAGACT
CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA

881 SACI,

902 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu
ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT
TGTCATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTGTTAGAA

931 SMAI XMAI,

962 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln
GAATTTTGGGAGGGCGTCTTTACAGGCTCACTCATATAGATGCCACTTTCTATCCCAG
CTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC

985 STUI,

1022 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla
ACAAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT
TGTTTCGTCTCACCCCTCTTGAAGGAATGGACCATCGCATGGTTCCGGTGGCACACGCGA

1069 DRA3,

1082 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys
AGGGCTCAAGCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTCCGCTCAAG
TCCCGAGTTCGGGGAGGGGGTAGCACCCCTGGTCTACACCTTCACAACTAAGCGGAGTTC

1142 ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle
CCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTTCAAGTAAATC
GGGTGGGAGGTACCCGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG

1150 NCOI,

1202 ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal
ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTGGCCGACCTGGAGGTC
TGGGACTGCGTGGGTGAGTGGTTTATGTACTGTACGTACAGCCGGCTGGACCTCCAG

1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

1262 ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu
GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCTGGCTGCTTTGGCCGCGTATTGCCTG
CAGTGCTCGTGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

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SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle
 1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA
 AGTTGTCCGACGCACCAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT
 1369 NAEI,
 ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu
 1382 CCTGACAGGGAAGTCCTCTACCGAGAGTTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA
 GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGGAGAGTCGTGAAT
 1385 DRD1,
 ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu
 1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCTC
 GGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG
 LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln
 1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCTGTGTCCAGACCAACTGGCAA
 GACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT
 1502 PSTI, 1507 TTH3I,
 LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu
 1562 AAACTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG
 TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC
 1565 XHOI, 1586 NDEI,
 AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla
 1622 GCGGGCTTGTCACCGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT
 CGCCCGAACAGTTGCGACGGACCATTTGGGGCGGTAACGAAGTAACTACCGAAAATGTCGA
 1643 BSTE2, 1677 ALWN1 PVU2,
 AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp
 1682 GCTGTACACGACCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG
 CGACAGTGGTCCGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC
 ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla
 1742 GTGGCTGCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT
 CACCGACGGGTGAGCGGGCGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA
 1794 ESP1,
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr
 1802 GGCGCCGCCATCGGCAGTGTTGGACTGGGGAAGGTCCTCATAGACATCCTTGCAGGGTAT
 CCGCGGCGGTAGCCGTCAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCATA
 1802 KAS1 NARI,
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer
 1862 GGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC
 CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG
 1878 SACI, 1899 BSPH1,

002211 547250

FIGURE 14 - Page 4

ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly
 1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCCTAGTCGGC
 TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG
 ^
 1928 TTH3I,
 ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp
 1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCCGGGCGAGGGGGCAGTGCAGTGG
 CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCCGTCACGTCACC
 ^ ^
 2004 NAEI, 2017 SMAI XMAI,
 MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal
 2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTCCCCACGCACTACGTCG
 TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCCTGATGCAC
 ^ ^
 2067 SMAI XMAI, 2093 DRA3,
 ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln
 2102 CCGGAGAGCGATGCAGCTGCCCGCTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG
 GGCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC
 ^ ^
 2115 PVU2, 2159 ALWN1,
 LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer
 2162 CTCCTGAGGCGACTGCACAGTGGATAAGCTCGGAGTGTAACCTCCATGCTCCGGTTCC
 GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG
 ^ ^
 2164 MST2, 2220 ECON1,
 TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu
 2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA
 ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT
 ^ ^
 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr
 2282 AAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCCTTTGTGTCCTGCCAGCGCGGGTAT
 TTTGATTGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTTCGCGCCCATG
 ^ ^ ^
 2285 ESP1, 2300 PVU2, 2310 BAMHI,
 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle
 2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC
 TTCCCCAGACCGCTCCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG
 ^ ^
 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet
 2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGTAC
 ^ ^ ^
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,
 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla
 2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCCTGTACCCCCCTTCTGCG
 ACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCGGGGACATGGGGGGAAGGACGC
 ^ ^
 2480 ASE1, 2497 APAI,
 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln

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Figure 1 consists of 12 sub-graphs, labeled (a) through (l), each representing a different fish species. The x-axis for all graphs is 'Year' from 1980 to 1990. The y-axis is 'Percentage of total catch' from 0 to 100. Each graph shows three data series: 'All gear' (solid line with circles), 'Trawl' (dashed line with squares), and 'Longline' (dotted line with triangles). The 'All gear' series is consistently the highest, often reaching 100%. The 'Trawl' and 'Longline' series are generally lower and show more variability. For example, in (a) Atlantic croaker, 'All gear' is around 80%, 'Trawl' is around 20%, and 'Longline' is around 10%. In (l) Atlantic halibut, 'All gear' is around 60%, 'Trawl' is around 30%, and 'Longline' is around 10%.

Variable	Mean		SD		t	p
	Control	Intervention	Control	Intervention		
Age	20.5	20.5	1.5	1.5	0.00	0.99
Gender	50	50	25	25	0.00	0.99
Marital status	50	50	25	25	0.00	0.99
Education	10.5	10.5	1.5	1.5	0.00	0.99
Religion	50	50	25	25	0.00	0.99
Occupation	50	50	25	25	0.00	0.99
Income	10.5	10.5	1.5	1.5	0.00	0.99
Health status	50	50	25	25	0.00	0.99
Family size	50	50	25	25	0.00	0.99
Parental education	10.5	10.5	1.5	1.5	0.00	0.99
Parental occupation	50	50	25	25	0.00	0.99
Parental income	10.5	10.5	1.5	1.5	0.00	0.99
Parental health status	50	50	25	25	0.00	0.99
Parental family size	50	50	25	25	0.00	0.99
Parental marital status	50	50	25	25	0.00	0.99
Parental gender	50	50	25	25	0.00	0.99
Parental age	20.5	20.5	1.5	1.5	0.00	0.99
Parental education	10.5	10.5	1.5	1.5	0.00	0.99
Parental occupation	50	50	25	25	0.00	0.99
Parental income	10.5	10.5	1.5	1.5	0.00	0.99
Parental health status	50	50	25	25	0.00	0.99
Parental family size	50	50	25	25	0.00	0.99
Parental marital status	50	50	25	25	0.00	0.99
Parental gender	50	50	25	25	0.00	0.99
Parental age	20.5	20.5	1.5	1.5	0.00	0.99
Parental education	10.5	10.5	1.5	1.5	0.00	0.99
Parental occupation	50	50	25	25	0.00	0.99
Parental income	10.5	10.5	1.5	1.5	0.00	0.99
Parental health status	50	50	25	25	0.00	0.99
Parental family size	50	50	25	25	0.00	0.99
Parental marital status	50	50	25	25	0.00	0.99
Parental gender	50	50	25	25	0.00	0.99
Parental age	20.5	20.5	1.5	1.5	0.00	0.99
Parental education	10.5	10.5	1.5	1.5	0.00	0.99
Parental occupation	50	50	25	25	0.00	0.99
Parental income	10.5	10.5	1.5	1.5	0.00	0.99
Parental health status	50	50	25	25	0.00	0.99
Parental family size	50	50	25	25	0.00	0.99
Parental marital status	50	50	25	25	0.00	0.99
Parental gender	50	50	25	25	0.00	0.99
Parental age	20.5	20.5	1.5	1.5	0.00	0.99
Parental education	10.5	10.5	1.5	1.5	0.00	0.99
Parental occupation	50	50	25	25	0.00	0.99
Parental income	10.5	10.5	1.5	1.5	0.00	0.99
Parental health status	50	50	25	25	0.00	0.99
Parental family size	50	50	25	25	0.00	0.99
Parental marital status	50	50	25	25	0.00	0.99
Parental gender	50	50	25	25	0.00	0.99
Parental age	20.5	20.5	1.5	1.5	0.00	0.99
Parental education	10.5	10.5	1.5	1.5	0.00	0.99
Parental occupation	50	50	25	25	0.00	0.99
Parental income	10.5	10.5	1.5	1.5	0.00	0.99
Parental health status	50	50	25	25	0.00	0.99
Parental family size	50	50	25	25	0.00	0.99
Parental marital status	50	50	25	25	0.00	0.99
Parental gender	50	50	25	25	0.00	0.99
Parental age	20.5	20.5	1.5	1.5		

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3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis
TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGCAGCCTGACGCCCCACAC
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGGGGTGTG
3816 HIND3,
3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla
TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC
AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG
3875 AAT2, 3890 BGLI,
3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp
GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACCAATAGAC
CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG
3962 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys
ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTTCAGCCTGAGAAGGGGGTTCGTAAG
TGATGGTAGTACCGATTCTTGCTCCAAAGACGCAAGTCGGACTCTTCCCCCAGCATTC
4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu
CCAGCTCGTCTCATCGTGTTCCTGATCTGGGCGTGCAGCGTGTGCGAAAAGATGGCTTTG
GGTCGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC
4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr
TACGACGTGGTTACAAAGCTCCCCTTGGCCGTGATGGGAAGCTCCTACGGATTCCAATAC
ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG
4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet
TCACCAGGACAGCGGGTTGAATTCTCTCGTGCAAGCGTGGAAGTCCAAGAAAACCCCAATG
AGTGGTCTCTCGCCCACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTTGGGGTTAC
4160 ECOR1,
4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr
GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG
CCCAAGAGCATACTATGGGCGACGAAACTGAGGTGTCACTGACTCTCGCTGTAGGCATGC
4229 DRD1, 4236 ALWN1,
4262 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer
GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCCAAGCCCGCTGGCCATCAAGTCC
CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTCTGGGCGCACCGGTAGTTCAGG
4301 BGLI, 4308 BALI,
4322 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly
CTCACCAGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC
GAGTGGCTCTCCGAAATACAACCCCGGGGAGAATGGTTAAGTTCCTCCCTCTTGACGCCG
4345 APAI,
4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys
TATCGCAGGTGCCGCGGAGCGGCGTACTGACAACTAGCTGTGGTAACACCCCTCACTTGC
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

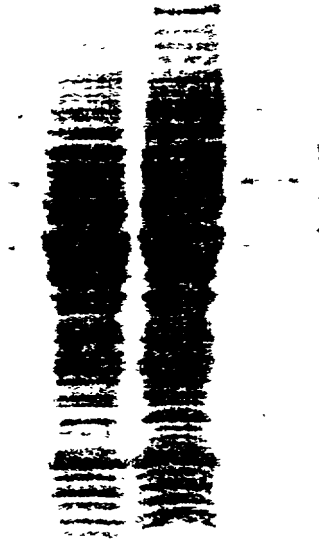
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FIGURE 14 - Page 9

5042 CCCTTGGCAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGCCCAGAGGA
GGGAACGCTCGAACCTCTGTGGCCCCGGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCTCT
5064 APAI, 5091 BALI,
GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA
CCGTCCCGACGGTATACACCGTTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT
5113 NDEI,
LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr
5162 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC
GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG
5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,
SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys
5222 AGCGGGGAGACATTTATCACAGCGTGTCTCATGCCCGGCCCGCTGGATCTGGTTTTGC
TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG
5240 DRA3,
LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgOP
5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCAACCGATGAATAGTCGAC
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTACTTATCAGCTG
5295 PSTI, 5336 SALI,

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FIGURE 15



SCANNED, # 14

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USSN 2302-1617
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FIGURE 16 - Page 1

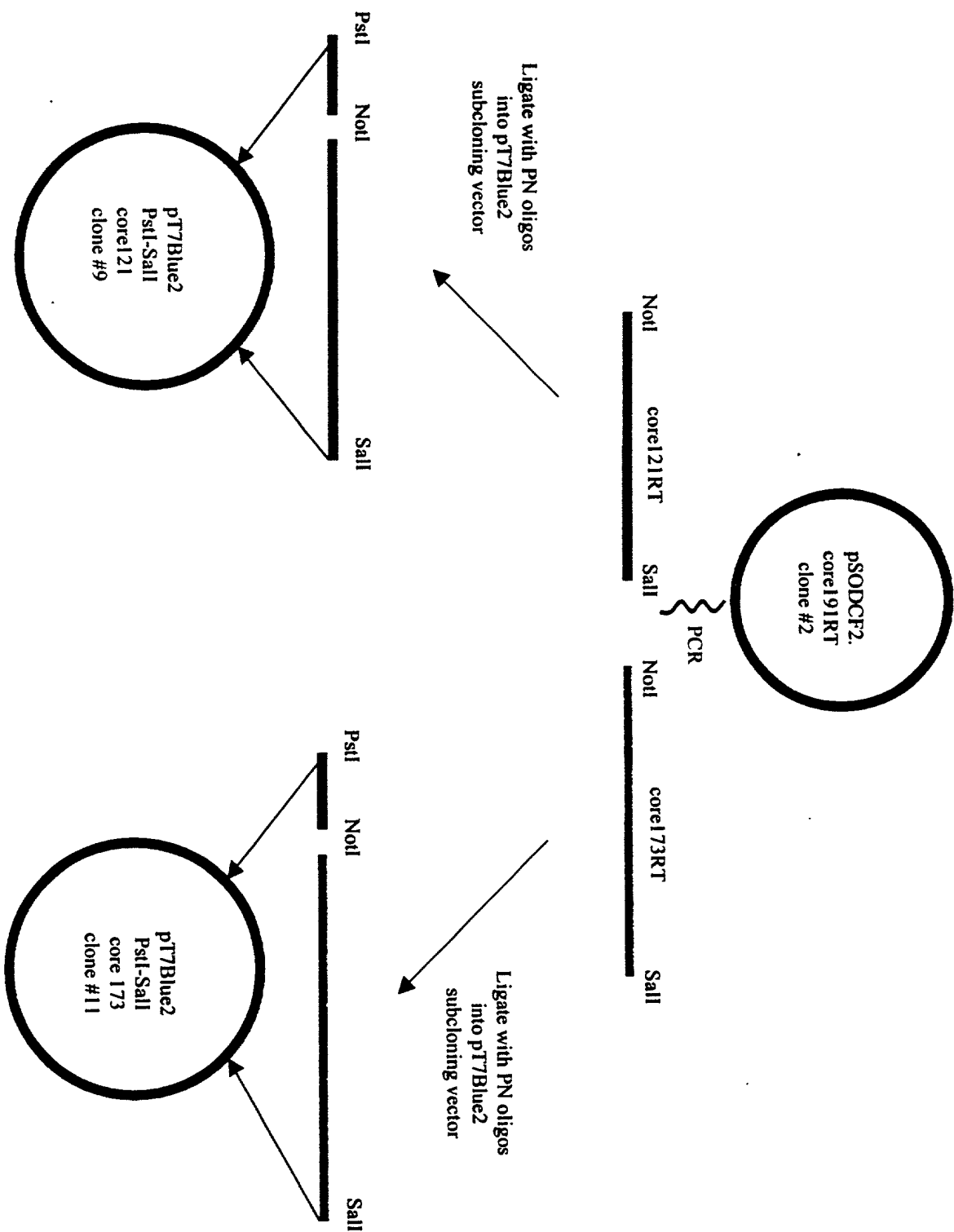
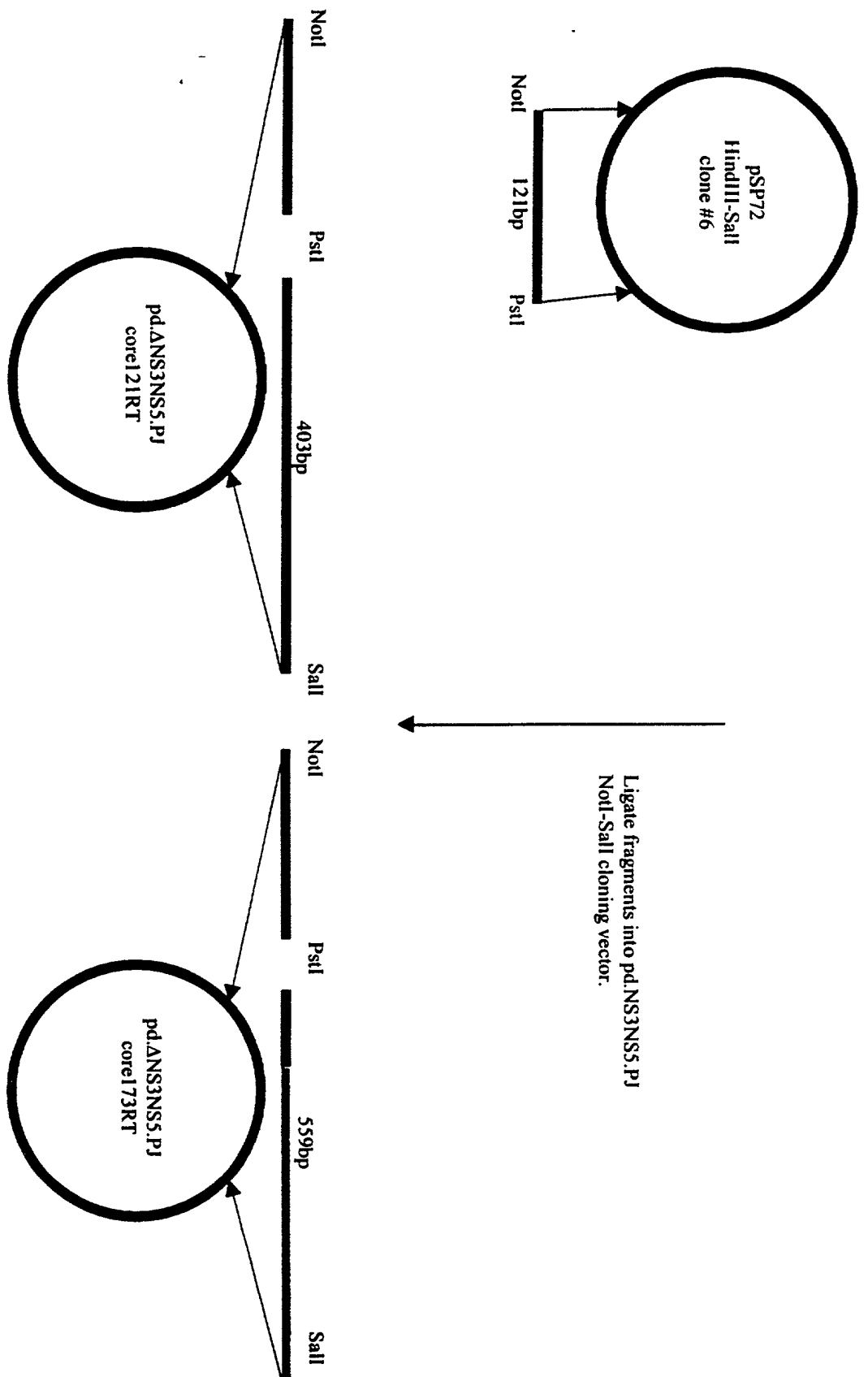


FIGURE 16 - Pa



Ligate fragments into pd,ΔNS3NS5,PJ
NotI-Sall cloning vector.

FIGURE 17 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn
2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC
TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG
^ ^ ^
1 HIND3, 24 NDEI, 52 SCAI,

ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp
62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT
GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA
^
116 CLAI,

ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr
122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTACTCCACC
GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG

TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys
182 TACGGCAAGTTCCTTGCCGACGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT
ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTATTAAACA

AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln
242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA
CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAACCTGTT

AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal
302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC
CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG
^
303 ALWN1,

ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe
362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT
TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA

TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis
422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTGAT
ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

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[illegible]

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal
 482 TCAAAGAAGAAGTGCACGAACTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG
 AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCACCAGCGCGCATGTTGTGTCGTCGTG
 CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC
 550 SAC2, 560 DRD1,
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA
 615 BSPH1,
 ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle
 662 ACGTGTGTACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTGAGACAATC
 TGCACACAGTGGGTCTGTCTCAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACCTCTGTTAG
 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG
 TGCAGAGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCTGACCGTCCCCCTTC
 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer
 782 CCAGGCATCTACAGATTGTGGCACCGGGGAGCGCCCCCTCCGGCATGTTGCACTCGTCC
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG
 816 BGLI, 833 DRD1,
 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGCCGAGACT
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAAGTGGGGGGGCTCTGA
 881 SACI,
 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT
 TGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCCTGGTAGAA
 931 SMAI XMAI,
 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTTCTATCCCAG
 CTTAAAACCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC
 985 STUI,
 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla
 1022 ACAAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT
 TGTTTCGTCTACCCCTCTTGGAAGGAATGGACCATCGCATGGTTCCGGTGGCACACGCGA
 1069 DRA3,
 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys
 1082 AGGGCTCAAGCCCTCCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCGCTCAAG

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp
1682 GCTGTCAACAGCCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG
CGACAGTGGTGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCAC

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla
1742 GTGGCTGCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT
CACCGACGGGTCGAGCGCGGGGGCCACGGCGATGACGGAACACCCGCGACCGAATCGA
1794 ESP1,
GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr
1802 GGC GCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCAGGGTAT
CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCATA
1802 KAS1 NARI,
GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer
1862 GGC GCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCCTCC
CCGCGCCCCGACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG
1878 SACI, 1899 BSPH1,
ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly
1922 ACGGAGGACCTGGTCAATCTACTGCCCCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC
TGCCTCTCGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG
1928 TTH3I,
ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp
1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCCGGCGAGGGGGCAGTGCAGTGG
CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCCGTCACGTCACC
2004 NAEI, 2017 SMAI XMAI,
MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal
2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCACGCACTACGTG
TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCGTGTATGCAC
2067 SMAI XMAI, 2093 DRA3,
ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln
2102 CCGGAGAGCGATGCAGCTGCCCGCTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG
GGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC
2115 PVU2, 2159 ALWN1,
LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer
2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC
GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG
2164 MST2, 2220 ECON1,
TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu
2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA
ACCGATTCCCTGTAGACCCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT
2282 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr
AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCTGCCAGCGCGGGTAT
TTTCGATTTCGAGTACGGTGTGACGCGACCCCTAGGGGAAACACAGGACGGTCGCGCCCAT
2285 ESP1, 2300 PVU2, 2310 BAMHI,

[illegible]

ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln
 2942 ACCGCTAACCATGACTCCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGGTTGGAGGATACCTCCGTC
 ^ ^
 2966 ESP1, 2969 SACI,
 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer
 3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTATTCTGGACTCC
 CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG
 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu
 3062 TTCGATCCGCTTGTGGCGGAGGAGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG
 AAGCTAGGCGAACACCGCCTCCTCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC
 ^
 3096 BGL2,
 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro
 3122 CGGAAGTCTCGGAGATTGCCCCAGGCCCTGCCCGTTTGGGCGCGGCCGGACTATAACCCC
 GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATATTGGGG
 ^ ^
 3143 ALWN1, 3164 EAG1 XMA3,
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro
 3182 CCGCTAGTGGAGACGTGGAAAAAGCCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCCG
 GGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC
 ^ ^
 3217 HGIE2, 3229 NCOI,
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu
 3242 CTTCCACCTCCAAAGTCCCTCCTGTGCCTCCGCCTCGGAAGAAGCGGACGGTGGTCTC
 GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer
 3302 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG
 ^ ^
 3332 SACI, 3346 HIND3,
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly
 3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCTTCTGGC
 AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro
 3422 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT
 ACGGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA
 ^
 3437 EAM11051,
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu
 3482 GGGGATCCGGATCTTAGCGACGGGTCATGGTCAACGGTCAGTAGTGAGGCCAACGCGGAG
 CCCCTAGGCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC
 ^ ^ ^
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla
 3542 GATGTGCTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGCACGCGG

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Figure 1 consists of 12 bar charts, labeled (a) through (l), each representing a different demographic or attitudinal variable. Each chart compares the percentage of Clinton supporters (light bars) and Gore supporters (dark bars) for that variable. The y-axis for all charts represents the percentage of respondents, ranging from 0 to 100.

- (a) Age:** Clinton supporters are more likely to be in the 18-29 age group, while Gore supporters are more likely to be in the 30-49 age group.
- (b) Sex:** Clinton supporters are more likely to be female, while Gore supporters are more likely to be male.
- (c) Education:** Clinton supporters are more likely to have a high school diploma or less education, while Gore supporters are more likely to have a college degree.
- (d) Income:** Clinton supporters are more likely to have a lower income, while Gore supporters are more likely to have a higher income.
- (e) Employment:** Clinton supporters are more likely to be employed, while Gore supporters are more likely to be unemployed.
- (f) Home ownership:** Clinton supporters are more likely to own their home, while Gore supporters are more likely to rent.
- (g) Marital status:** Clinton supporters are more likely to be married, while Gore supporters are more likely to be single.
- (h) Political affiliation:** Clinton supporters are more likely to be Democrats, while Gore supporters are more likely to be Republicans.
- (i) Party identification:** Clinton supporters are more likely to identify with the Democratic Party, while Gore supporters are more likely to identify with the Republican Party.
- (j) Trust in Clinton:** Clinton supporters are more likely to trust Clinton, while Gore supporters are less likely to trust Clinton.
- (k) Confidence in Clinton:** Clinton supporters are more likely to have confidence in Clinton, while Gore supporters are less likely to have confidence in Clinton.
- (l) Confidence in Gore:** Clinton supporters are less likely to have confidence in Gore, while Gore supporters are more likely to have confidence in Gore.

AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn
3602 GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT
CGCCTTCTTGCTTTGACGGGTAGTTACGTGATTTCGTTGAGCAACGATGCAGTGGTGTTA

LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp
3662 TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC
AACCACATAAGGTGGTGGAGTGCCTCACGAACGGTTTCCGCTCTTCTTCAGTGTAAACTG

3722 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla
AGACTGCAAGTTCCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG
TCTGACGTTCAAGACCTGTCGGTAATGGTCCTGCATGAGTTCCTCCAATTCGTCGCCGC

3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis
TCAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGCAGCCTGACGCCCCACAC
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGGGGTGTG

3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla
TCAGCCAAATCCAAGTTTGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC
AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG

ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp
3902 GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCAATAGAC
CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG

ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys
3962 ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGGTCGTAAG
TGATGGTAGTACCGATTCTTGCTCCAAAGACGCAAGTCGGACTCTCCCCCAGCATTC

ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu
4022 CCAGCTCGTCTCATCGTGTTCCCGGATCTGGGCGTGCGCGTGTGCGAAAGATGGCTTTG
GGTCGAGCAGAGTAGCACAAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAC

4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr
TACGACGTGGTTACAAAGCTCCCCTTGCCGTGATGGGAAGCTCCTACGGATTCCAATAC
ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG

4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet
TCACCAGGACAGCGGGTTGAATTCTCTGTCGAAGCGTGAAGTCCAAGAAAACCCCAATG
AGTGGTCTGTGCGCCCAACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTGGGGTTAC

GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr
4202 GGGTTCTCGTATGATACCCGTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG
CCCAAGAGCATACTATGGGCGACGAAACTGAGGTGTCAGTGACTCTCGCTGTAGGCATGC

4862 AGGGACCCAGCTTGAACACCGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA
TCCCTGGTCTGAACTTGTCCGGGAGCTAACGCTCTAGATGCCCCGGACGATGAGGTATCTT
4893 BGL2,
ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis
4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC
GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTTCGCGTAAAGTGAGGTG
4954 NCOI,
SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro
4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAACTTGGGGTACCG
TCAATGAGAGGTCCACTTTAGTTATCCACCGCGTACGGAGTCTTTTGAACCCCATGGC
5015 SPHI, 5035 KPNI,
ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly
5042 CCCTTGCGAGCTTGGAGACACCGGGCCCGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA
GGGAACGCTCGAACCTCTGTGGCCCCGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCCT
5064 APAI, 5091 BALI,
GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCACTGGGCAGTAAGAACAAGCTCAA
CCGTCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT
5113 NDEI,
LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr
5162 CTCACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTTCACGGCTGGCTAC
GAGTGAGGTTATCGCCGGCGACCGGTGACCTGAACAGGCCGACCAAGTGCCGACCGATG
5174 NOTI, 5175 EAG1 XMA3, 5182 BALI, 5186 PVU2,
SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys
5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCGGCCCCGCTGGATCTGGTTTTGC
TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAACG
5240 DRA3,
LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn
5282 CTACTCCTGCTTGCTGTCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCACGAAT
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA
5295 PSTI,
ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe
5342 CCTAAACCTCAAAGAAAGACCAACGTAACACCAACCGGCGGCCGAGGACGTCAAGTTC
GGATTTGGAGTTTCTTTCTGGTTTGCAATTGTGGTTGGCGCCGGCGTCTGCAGTTCAAG
5380 NOTI, 5381 EAG1 XMA3, 5390 AAT2, 5401 SMAI XMAI,
ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu
5402 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTGTGCCGCGCAGGGGCCCTAGATTG
GGCCCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC

[illegible]

5702 AC
TG

Parameter	Value	Unit
Initial temperature	25	°C
Initial concentration	0.1	mol/L
Reaction time	0-10	min
Reaction temperature	25	°C
Reaction pressure	1	atm
Reaction volume	10	L
Reaction rate	0.01	mol/L·min
Reaction order	1	
Reaction mechanism	First-order	
Reaction activation energy	10	kJ/mol
Reaction equilibrium constant	1	
Reaction half-life	10	min
Reaction rate constant	0.01	min ⁻¹
Reaction rate constant at 25°C	0.01	min ⁻¹
Reaction rate constant at 30°C	0.02	min ⁻¹
Reaction rate constant at 35°C	0.04	min ⁻¹
Reaction rate constant at 40°C	0.08	min ⁻¹
Reaction rate constant at 45°C	0.15	min ⁻¹
Reaction rate constant at 50°C	0.3	min ⁻¹
Reaction rate constant at 55°C	0.6	min ⁻¹
Reaction rate constant at 60°C	1.2	min ⁻¹
Reaction rate constant at 65°C	2.4	min ⁻¹
Reaction rate constant at 70°C	4.8	min ⁻¹
Reaction rate constant at 75°C	9.6	min ⁻¹
Reaction rate constant at 80°C	19.2	min ⁻¹
Reaction rate constant at 85°C	38.4	min ⁻¹
Reaction rate constant at 90°C	76.8	min ⁻¹
Reaction rate constant at 95°C	153.6	min ⁻¹
Reaction rate constant at 100°C	307.2	min ⁻¹
Reaction rate constant at 105°C	614.4	min ⁻¹
Reaction rate constant at 110°C	1228.8	min ⁻¹
Reaction rate constant at 115°C	2457.6	min ⁻¹
Reaction rate constant at 120°C	4915.2	min ⁻¹
Reaction rate constant at 125°C	9830.4	min ⁻¹
Reaction rate constant at 130°C	19660.8	min ⁻¹
Reaction rate constant at 135°C	39321.6	min ⁻¹
Reaction rate constant at 140°C	78643.2	min ⁻¹
Reaction rate constant at 145°C	157286.4	min ⁻¹
Reaction rate constant at 150°C	314572.8	min ⁻¹
Reaction rate constant at 155°C	629145.6	min ⁻¹
Reaction rate constant at 160°C	1258291.2	min ⁻¹
Reaction rate constant at 165°C	2516582.4	min ⁻¹
Reaction rate constant at 170°C	5033164.8	min ⁻¹
Reaction rate constant at 175°C	10066329.6	min ⁻¹
Reaction rate constant at 180°C	20132659.2	min ⁻¹
Reaction rate constant at 185°C	40265318.4	min ⁻¹
Reaction rate constant at 190°C	80530636.8	min ⁻¹
Reaction rate constant at 195°C	161061273.6	min ⁻¹
Reaction rate constant at 200°C	322122547.2	min ⁻¹
Reaction rate constant at 205°C	644245094.4	min ⁻¹
Reaction rate constant at 210°C	1288490188.8	min ⁻¹
Reaction rate constant at 215°C	2576980377.6	min ⁻¹
Reaction rate constant at 220°C	5153960755.2	min ⁻¹
Reaction rate constant at 225°C	10307921510.4	min ⁻¹
Reaction rate constant at 230°C	20615843020.8	min ⁻¹
Reaction rate constant at 235°C	41231686041.6	min ⁻¹
Reaction rate constant at 240°C	82463372083.2	min ⁻¹
Reaction rate constant at 245°C	164926744166.4	min ⁻¹
Reaction rate constant at 250°C	329853488332.8	min ⁻¹
Reaction rate constant at 255°C	659706976665.6	min ⁻¹
Reaction rate constant at 260°C	1319413953331.2	min ⁻¹
Reaction rate constant at 265°C	2638827906662.4	min ⁻¹
Reaction rate constant at 270°C	5277655813324.8	min ⁻¹
Reaction rate constant at 275°C	10555311626649.6	min ⁻¹
Reaction rate constant at 280°C	21110623253299.2	min ⁻¹
Reaction rate constant at 285°C	42221246506598.4	min ⁻¹
Reaction rate constant at 290°C	84442493013196.8	min ⁻¹
Reaction rate constant at 295°C	168884986026393.6	min ⁻¹
Reaction rate constant at 300°C	337769972052787.2	min ⁻¹
Reaction rate constant at 305°C	675539944105574.4	min ⁻¹
Reaction rate constant at 310°C	1351079888211148.8	min ⁻¹
Reaction rate constant at 315°C	2702159776422297.6	min ⁻¹
Reaction rate constant at 320°C	5404319552844595.2	min ⁻¹
Reaction rate constant at 325°C	10808639105689190.4	min ⁻¹
Reaction rate constant at 330°C	21617278211378380.8	min ⁻¹
Reaction rate constant at 335°C	43234556422756761.6	min ⁻¹
Reaction rate constant at 340°C	86469112845513523.2	min ⁻¹
Reaction rate constant at 345°C	172938225691027046.4	min ⁻¹
Reaction rate constant at 350°C	345876451382054092.8	min ⁻¹
Reaction rate constant at 355°C	691752902764108185.6	min ⁻¹
Reaction rate constant at 360°C	1383505805528216371.2	min ⁻¹
Reaction rate constant at 365°C	2767011611056432742.4	min ⁻¹
Reaction rate constant at 370°C	5534023222112865484.8	min ⁻¹
Reaction rate constant at 375°C</		

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn
2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC
TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG
^ ^ ^
1 HIND3, 24 NDEI, 52 SCAI,

ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp
62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT
GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA
^ ^
116 CLAI,

ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr
122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCACGTACTCCACC
GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGATGAGGTGG

TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys
182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT
ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCAATACTGTATTATTAAACA

AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln
242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA
CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAC TGTT

AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal
302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC
CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG
^ ^
303 ALWN1,

ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe
362 ACTGTGCCCCATCCCAACATCGAGGAGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT
TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA

TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis
422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGGAGACATCTCATCTTCTGTCAT
ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal
482 TCAAAGAAGAAGTGCGACGAACTCGCCGCAAAGCTGGTCGCATTGGGCATCAATGCCGTG
AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC

AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal
542 GCCTACTACCGCGGTCTTGACGTGTCGTCATCCCGACCAGCGGCGATGTTGTGTCGTCGTG
CGGATGATGGCGCCAGAACTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC
^ ^
550 SAC2, 560 DRD1,

AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn
602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT
CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA
^ ^
615 BSPH1,

FIGURE 18 - Page 2

ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle
 662 ACGTGTGTCACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTCACCATTGAGACAATC
 TGCACACAGTGGGTCTGTCTCAGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACTCTGTTAG

 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG
 TGGCAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCCTGACCGTCCCCCTTC

 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer
 782 CCAGGCATCTACAGATTTGTGGCACCAGGGGAGCGCCCTCCGGCATGTTGACTCGTCC
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG
 ^ ^
 816 BGLI, 833 DRD1,

 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGAGACT
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGCGGCTCTGA
 ^
 881 SACI,

 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT
 TGTCATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTCTGGTAGAA
 ^
 931 SMAI XMAI,

 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCCACTTTCTATCCCAG
 CTTAAACCCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC
 ^
 985 STUI,

 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla
 1022 ACAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT
 TGTTTCGTCTCACCCCTCTTGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCGA
 ^
 1069 DRA3,

 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys
 1082 AGGGCTCAAGCCCCCTCCCCATCGTGGGACCAGATGTGGAAGTGTTGATTGCGCTCAAG
 TCCCGAGTTCGGGGAGGGGGTAGCACCCCTGGTCTACACCTTCACAACTAAGCGGAGTTC

 ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle
 1142 CCCACCCTCCATGGGCCAACACCCCTGCTATACAGACTGGGCGCTGTTGAGAATGAAATC
 GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCGCGACAAGTCTTACTTTAG
 ^
 1150 NCOI,

 ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal
 1202 ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTGGAGGTC
 TGGGACTGCGTGGGTGAGTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG
 ^ ^ ^ ^ ^
 1230 BSPH1, 1234 DRD1, 1237 AVA3, 1245 EAG1 XMA3, 1250 DRD1,

 ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu
 1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCCTGGCTGCTTTGGCCGCGTATTGCGCTG

FIGURE 18 - Page 3

CAGTGTCTGCTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC
 SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle
 1322 TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA
 AGTTGTCCGACGCACCAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT
 1369 NAEI,
 ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu
 1382 CCTGACAGGGAAGTCCTCTACCGAGAGTTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA
 GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCAGAGAGTCGTGAAT
 1385 DRD1,
 ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu
 1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCTC
 GGCATGTAGCTCGTTCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCGGGAGCCGGAG
 LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln
 1502 CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCCTGCTGTCCAGACCACTGGCAA
 GACGTCTGGCGCAGGGCAGTCCGTCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT
 1502 PSTI, 1507 TTH3I,
 LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu
 1562 AAACCTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG
 TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCTATGTTATGAAC
 1565 XHOI, 1586 NDEI,
 AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla
 1622 GCGGGCTTGTCAACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT
 CGCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAACTACCGAAAATGTCTGA
 1643 BSTE2, 1677 ALWN1 PVU2,
 AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp
 1682 GCTGTCAACAGCCCACTAACCACTAGCCAAACCTCCTCTTCAACATATTGGGGGGTGG
 CGACAGTGGTCGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC
 ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla
 1742 GTGGCTGCCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT
 CACCGACGGGTGAGCGGGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA
 1794 ESP1,
 GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr
 1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGAGGGGTAT
 CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCAT
 1802 KAS1 NARI,
 GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer
 1862 GGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCCTCC
 CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG
 1878 SACI, 1899 BSPH1,

00221154250

ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly
1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC
TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG
1928 TTH3I,
ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp
1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGCGAGGGGGCAGTGCAGTGG
CACCAGACACGTCGTTATGACGGCGCCGTGCAACCGGGCCCGCTCCCCCGTCACGTCAAC
2004 NAEI, 2017 SMAI XMAI,
MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal
2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTTCCCCCAGCACTACGTG
TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCGTGATGCAC
2067 SMAI XMAI, 2093 DRA3,
ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln
2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCGTA
GGCCTCTCGCTACGTGACGGGCGCAGTGACGGTATGAGTCGTGCGAGTGACATTGGGTC
2115 PVU2, 2159 ALWN1,
LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer
2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC
GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG
2164 MST2, 2220 ECON1,
TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu
2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA
ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT
LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr
2282 AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCCTTTGTGTCTGCCAGCGCGGGTAT
TTTCGATTGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTCGCGCCCAT
2285 ESP1, 2300 PVU2, 2310 BAMHI,
LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle
2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC
TTCCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG
ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet
2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCTAGGACCTGCAGGAACATG
TGACCTGTACAGTTTTTGCCTGTCTACTCCTAGCAGCCAGGATCCTGGACGTCCTTGATC
2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,
TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla
2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCCCTGTACCCCCCTTCTGCG
ACCTCACCTGGAAGGGGTAAATTACGGATGTGTTGCCCGGGGACATGGGGGGAAGGACGC
2480 ASE1, 2497 APAI,

ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln
2522 CCGAACTACACGTTCCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG
GGCTTGATGTGCAAGCGCGATACCTCCCACAGACGTCTCCTTATGCACCTCTATTCCGTC
2553 PSTI,
ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln
2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCCGTGCCAG
CACCCCTGAAGGTGATGCACTGCCCATACTGATGACTGTTAGAATTTACGGGCACGGTC
2594 DRA3,
ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro
2642 GTCECATCGCCCCGAATTTTTCACAGAATTGGACGGGGTGGCCTACATAGGTTTGGCCCC
CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGCGGATGTATCCAAACGCGGG
ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro
2702 CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTCAGAGTAGGACTCCACGAATACCCG
GGGACGTTGCGGGAACGACGCCCTCCTCCATAGTAAGTCTCATCCTGAGGTGCTTATGGGC
2757 HGIE2,
ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu
2762 GTAGGGTCGAATTACCTTGCGAGCCCGAACC GGACGTGGCCGTGTTGACGTCCATGCTC
CATCCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAAC TG CAGGTACGAG
2809 AAT2,
ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro
2822 ACTGATCCCTCCCATATAACAGCAGAGGCGGCCGGCGGAAGTTGGCGAGGGGATCACCC
TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCCGCTTCCAACCGCTCCCCTAGTGGG
2850 EAG1 XMA3,
ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys
2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC
GGGAGACACCGGTCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG
2889 BALI, 2903 NHEI,
ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln
2942 ACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG
TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGGTTGGAGGATACCTCCGTC
2966 ESP1, 2969 SACI,
GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer
3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC
CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG
3062 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu
TTCGATCCGCTTGTTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG
AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC
3096 BGL2,
ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro

3122 CGGAAGTCTCGGAGATTTCGCCAGGCCCTGCCCCGTTTGGGCGCGGCCGGACTATAAACC
GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCCTGATATTGGG
3143 ALWN1, 3164 EAG1 XMA3,
ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro
3182 CCGCTAGTGGAGACGTGGAAAAAGCCCCACTACGAACCACCTGTGGTCCATGGCTGCCCG
GGCGATCACCTCTGCACCTTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGG
3217 HGIE2, 3229 NCOI,
LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu
3242 CTTCCACCTCCAAAGTCCCTCCTGTGCCTCCGCTCGGAAGAAGCGGACGGTGGTCCCTC
GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCTGCCACCAGGAG
ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer
3302 ACTGAATCAACCCTATCTACTGCCTTGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC
TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTTCGAAACCGTCGAGG
3332 SAC1, 3346 HIND3,
SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly
3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCCCCCCTTCTGGC
AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG
CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro
3422 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCCCTGGAGGGGGAGCCT
ACGGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA
3437 EAM11051,
GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu
3482 GGGGATCCGGATCTTAGCGACGGGTGATGGTCAACGGTCAGTAGTGAGGCCAACGCGGAG
CCCCTAGGCCCTAGAATCGCTGCCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC
3484 BAMHI, 3485 BSAB1, 3487 BSPE1,
AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla
3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGACAGGCGCACTCGTCACCCCGTGCGCC
CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCTGAGCAGTGGGGCACGCGG
3589 DRA3, 3600 SAC2,
AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn
3602 GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT
CGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTGCTTGAGCAACGATGCAGTGGTGTTA
3611 ALWN1, 3655 PFLM1,
LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp
3662 TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC
AACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTAGTGTAAGTGT
3681 DRA3,
ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla
3722 AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGGC

4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys
TATCGCAGGTGCCGCGAGCGGGCTACTGACAACTAGCTGTGGTAACACCCTCACTTGC
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal
 4442 TACATCAAGGCCCGGGCAGCCTGTCTGAGCCGCAGGGCTCCAGGACTGCACCATGCTCGTG
 ATGTAGTTCGGGGCCCGTCGGACAGCTCGGCGTCCCGAGGTCCTGACGTGGTACGAGCAC
 ^
 4452 SMAI XMAI,
 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer
 4502 TGTGGCGACGACTTAGTTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCGGCGAGC
 ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCTCTCTGCGCCGCTCG
 ^ ^
 4508 DRD1, 4511 TTH3I,
 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln
 4562 CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCCCACAA
 GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGGTGT
 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp
 4622 CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTCTGCGCCACGAC
 GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTGCACAGTCAGCGGGTGTCTG
 ^
 4637 SACI,
 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla
 4682 GGCGCTGGAAAGAGGGTCTACTACCTACCCGTGACCCACAACCCCCCTCGCGAGAGCT
 CCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGCTCTCGA
 ^
 4731 NRUI,
 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe
 4742 GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT
 CGCACCTCTGTCTTCTGTGTGAGGTGAGTTAAGGACCGATCCGTTGTATTAGTACAAA
 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla
 4802 GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTCTTTAGCGTCTTTATAGCC
 CGGGGGTGTGACACCCGCTCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG
 ^ ^
 4806 PFLM1, 4807 DRA3,
 ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu
 4862 AGGGACCACTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA
 TCCCTGGTTCGAACCTGTCCGGGAGCTAACGCTCTAGATGCCCCGACGATGAGGTATCTT
 ^
 4893 BGL2,
 ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis
 4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC
 GGTGACCTAGATGGAGTTAGTAAGTTTCTGAGGTACCGAGTCCGCTAAAAGTGAGGTG
 ^
 4954 NCOI,
 SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro
 4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTTGGGGTACCG
 TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC
 ^ ^
 5015 SPHI, 5035 KPNI,

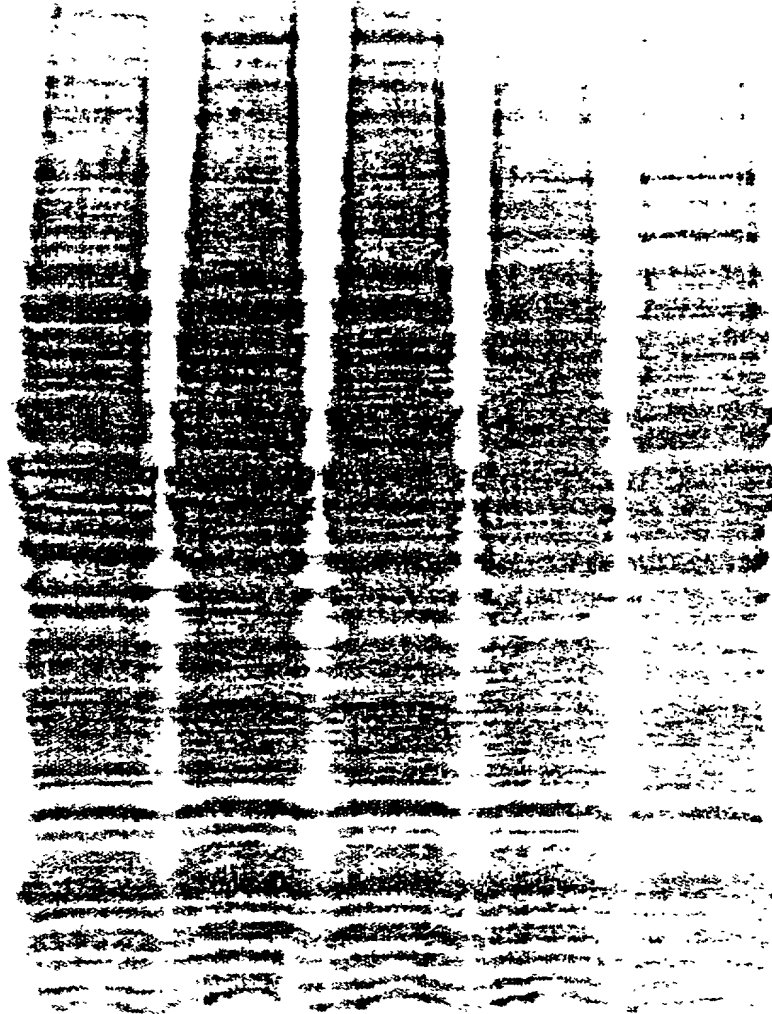
FIGURE 18 - Page 9

5042 ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly
 CCCTTGCGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA
 GGAACGCTCGAACCTCTGTGGCCCGGCGCTCGCAGGCGCGATCCGAAGACCGGTCTCCT
 5064 APAI, 5091 BALI,
 5102 GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys
 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA
 CCGTCCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT
 5113 NDEI,
 5162 LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr
 CTCACTCCAATAGCGGCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC
 GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCGGACCAAGTGCCGACCGATG
 5174 NOTI, 5175 EAG1 XMA3, 5182 BALI, 5186 PVU2,
 5222 SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys
 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCCGCCCCGCTGGATCTGGTTTTGC
 TCGCCCCCTCTGTAAATAGTGTGCGCACAGAGTACGGGCGGGGCGACCTAGACCAAAACG
 5240 DRA3,
 5282 LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn
 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCAGGAAT
 GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA
 5295 PSTI,
 5342 ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe
 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGCGCGCGCAGGACGTCAAGTTC
 GGATTTGGAGTTTCTTTCTGGTTTGATTGTGGTTGGCCGCGCGCGCTCCTGCAGTTCAAG
 5380 NOTI, 5381 EAG1 XMA3, 5390 AAT2, 5401 SMAI XMAI,
 5402 ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu
 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTTGCCGCGCAGGGGGCCCTAGATTG
 GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC
 5449 APAI,
 5462 GlyValArgAlaThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro
 GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTGCAACCTCGAGGTAGACGTGAGCCT
 CCACACGCGCGCTGCTCTTTCTGAAGGCTCGCCAGCGTTGGAGCTCCATCTGCAGTCGGA
 5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,
 5522 IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGlyTyrProTrpPro
 ATCCCCAAGGCTCGTCCGCCCCGAGGGCAGGACCTGGGCTCAGCCCCGGGTACCCTTGGCCCC
 TAGGGGTTCCGAGCAGCCGGGCTCCCGTCTGGACCCGAGTCGGGCCCCATGGGAACCGG
 5548 ALWN1, 5558 ESP1, 5564 SMAI XMAI, 5568 KPNI,
 5582 LeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrpLeuLeuSerProArgGlySerArg
 CTCTATGGCAATGAGGGCTGCGGGTGGGCGGATGGCTCCTGTCTCCCCGTGGCTCTCGG
 GAGATACCGTTACTCCCCGACGCCACCCGCCCTACCGAGGACAGAGGGGCACCGAGAGCC

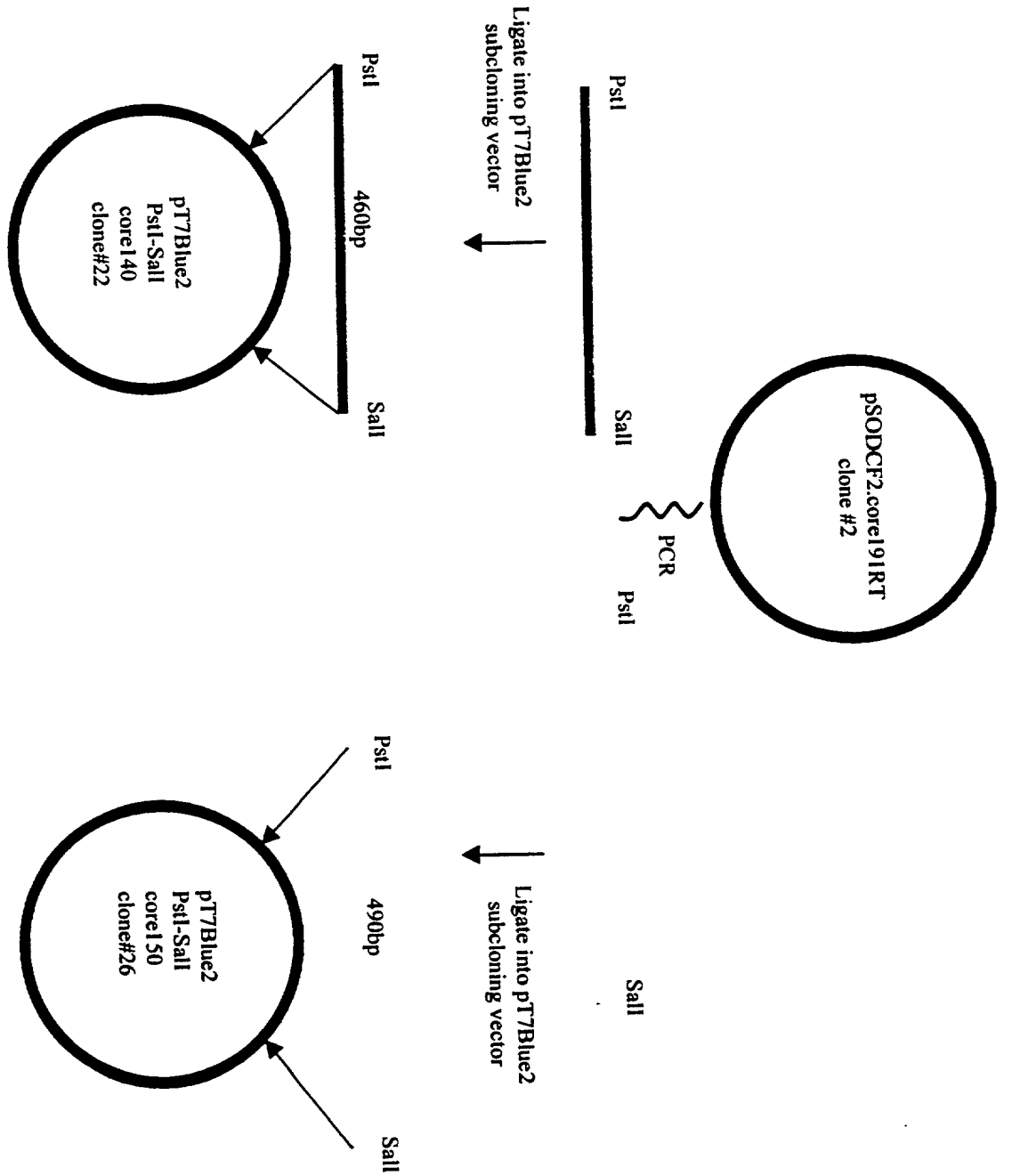
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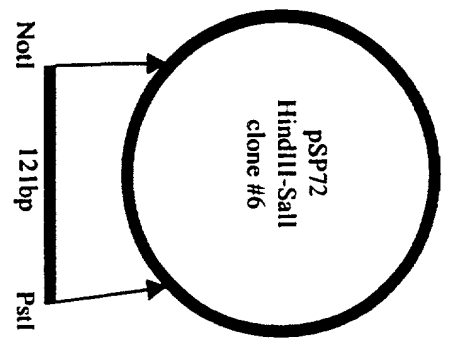
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FIGURE 19



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Ligate fragments into pd.NS3NSS5.PJ
NotI-Sall cloning vector.

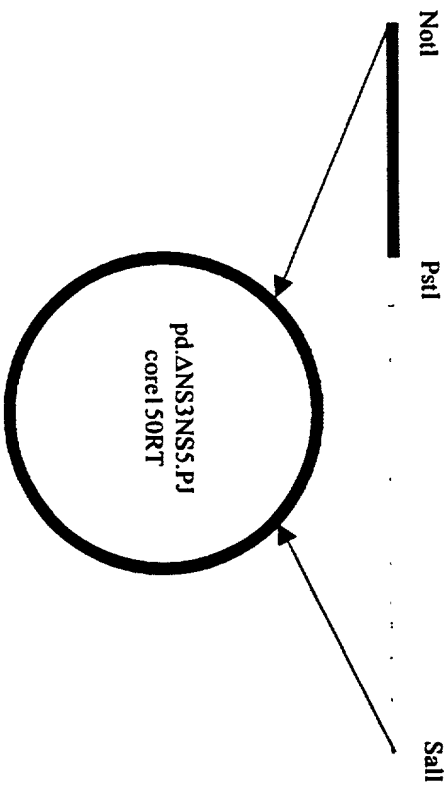
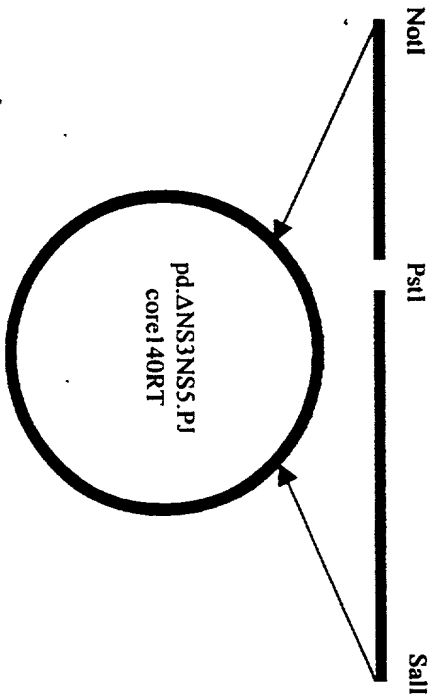


FIGURE 21 - Page 1

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn
2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC
TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG
^ ^ ^
1 HIND3, 24 NDEI, 52 SCAI,
ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp
62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT
GGGAGACAACGACGTTGTGACCCGAAACCAGAATGTACAGGTTCCGAGTACCCTAGCTA
^
116 CLAI,
ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr
122 CCTAACATCAGGACCGGGTGAGAACAATTACCACTGGCAGCCCCATCAGTACTCCACC
GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGCATGAGGTGG
TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys
182 TACGGCAAGTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT
ATGCCGTTCAAGGAACGGCTGCCGCCACGAGCCCCCGCGAATACTGTATTATTAAACA
AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln
242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA
CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT
AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal
302 GCAGAGACTGCGGGGCGGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC
CGTCTCTGACGCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG
^
303 ALWN1,
ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe
362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT
TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA
TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis
422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT
ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

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SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal
 482 TCAAAGAAGAAGTGCACGAACTCGCCGCAAAGCTGGTGCATTGGGCATCAATGCCGTG
 AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTATCCCGACCAGCGGCGATGTGTGCGTCTGTG
 CGGATGATGGCGCCAGA[^]ACTGCACAGGCAGTAGGGCTGGTTCGCCGCTACAACAGCAGCAC
 550 SAC2, 560 DRD1,
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT
 CGTTGGCTACGGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA
 615 BSPH1,
 ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle
 662 ACGTGTGTACCCAGACAGTCGATTTTCAGCCTTGACCCTACCTTACCATTGAGACAATC
 TGCACACAGTGGGTCTGTACAGCTAAAGTCGGA[^]ACTGGGATGGAAGTGGTAACTCTGTTAG
 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys
 722 ACGCTCCCCAAGATGCTGTCTCCCGCACTCAACGTGGGGGAGGACTGGCAGGGGGGAA
 TGCGAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCCGTCTGACCGTCCCCCTTC
 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer
 782 CCAGGCATCTACAGATTTGTGGCACCGGGGGAGCGCCCCCTCCGGCATGTTGACTCGTCC
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG
 816 BGLI, 833 DRD1,
 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCGCCGAGACT
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGA[^]GTGCGGGCGGCTCTGA
 881 SACI,
 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT
 TGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCTCTGGTAGAA
 931 SMAI XMAI,
 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCACTTCTATCCCAG
 CTTAA[^]AAACCCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC
 985 STUI,
 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla
 1022 ACAAAGCAGAGTGGGGAGAACCTTCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT
 TGTTTCGTCTACCCCTCTTGGGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCGA
 1069 DRA3,
 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys
 1082 AGGGGCTCAAGCCCCCTCCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTTCGCCTCAAG

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp
1682 GCTGTCACCAGCCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG
CGACAGTGGTCGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla
1742 GTGGCTGCCAGCTCGCCGCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT
CACCGACGGGTCGAGCGGCGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA
1794 ESP1,
GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr
1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCAGGGTAT
CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCATA
1802 KAS1 NARI,
GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer
1862 GGCGCGGGCGTGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCTCC
CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG
1878 SACI, 1899 BSPH1,
ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly
1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC
TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG
1928 TTH3I,
ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp
1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCCGGGCGAGGGGGCAGTGCACTGG
CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCCGTCACGTCACC
2004 NAEI, 2017 SMAI XMAI,
MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal
2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTCCCCCACGCACTACGTG
TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGTGCGTGATGCAC
2067 SMAI XMAI, 2093 DRA3,
ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln
2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG
GGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC
2115 PVU2, 2159 ALWN1,
LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer
2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTAACCACTCCATGCTCCGGTTCC
GAGGACTCCGCTGACGTGGTCACCTATTTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG
2164 MST2, 2220 ECON1,
TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu
2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA
ACCGATTCCCTGTAGACCCTGACCTATACGCTCCACAACCTCGCTGAAATTCTGGACCGAT
2282 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr
AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCCTTTGTGTCCTGCCAGCGGGGTAT
TTTCGATTTCGAGTACGGTGTGACGGACCCTAGGGGAAACACAGGACGGTTCGCGCCCAT
2285 ESP1, 2300 PVU2, 2310 BAMHI,

LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle
 2342 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC
 TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG
 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet
 2402 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCTTAGGACCTGCAGGAACATG
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCTTGTAC
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,
 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla
 2462 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCTGTACCCCCCTTCTGCG
 ACCTCACCTGGAAGGGGTAATTACGGATGTGGTGCCCGGGACATGGGGGAAGGACGC
 2480 ASE1, 2497 APAI,
 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln
 2522 CCGAACTACACGTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG
 GGCTTGATGTGCAAGCGGATACCTCCACAGACGTCTCCTTATGCACCTCTATTCCGTC
 2553 PSTI,
 ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln
 2582 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG
 CACCCCCTGAAGGTGATGCACTGCCATACTGATGACTGTTAGAATTTACGGGCACGGTC
 2594 DRA3,
 ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro
 2642 GTCCCATCGCCCGAATTTTTCACAGAATTGGACGGGTGCGCCTACATAGGTTTGCGCC
 CAGGGTAGCGGGCTTAAAAAGTGCTTAACCTGCCCCACGGGATGTATCCAAACGCGG
 ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro
 2702 CCCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTAGAGTAGGACTCCACGAATACCCG
 GGGACGTTGCGGAACGACGCCCTCCTCCATAGTAAGTCTCATCTGAGGTGCTTATGGGC
 2757 HGIE2,
 ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu
 2762 GTAGGGTCGCAATTACCTTGCGAGCCCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC
 CATCCCAGCGTTAATGGAACGCTCGGGCTTGCCCTGCACCGGCACAACCTGACGGTACGAG
 2809 AAT2,
 ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro
 2822 ACTGATCCCTCCCATATAACAGCAGAGGCGGCCGGGCGAAGGTTGGCGAGGGGATCACCC
 TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCGCTTCCAACCGCTCCCCTAGTGGG
 2850 EAG1 XMA3,
 ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys
 2882 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC
 GGGAGACACCGGTCGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCGGTTGAACG
 2889 BALI, 2903 NHEI,

ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuTrpArgGin
2942 ACCGCTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAT
TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTGGAGGATACCTCCGTC
 ^ ^
2966 ESP1, 2969 SACI,

GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer
3002 GAGATGGGCGGCAACATCACCCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC
CTCTACCCGCCGTGTAGTGGTCCCCA ACTCAGTCTTTTGTTCACCACTAAGACCTGAGG

PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu
3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGGAGATCTCCGTACCCGCAGAAATCCTG
AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC
 ^
3096 BGL2,

ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro
3122 CGGAAGTCTCGGAGATTGCCCCAGGCCCTGCCCGTTTTGGGCGCGGCCGGACTATAACCCC
GCCTTCAGAGCCTCTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGGCCTGATATTGGGG
 ^ ^
3143 ALWN1, 3164 EAG1 XMA3,

ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro
3182 CCGCTAGTGGAGACGTGGAAAAAGCCCGACTACGAACCACCTGTGGTCCATGGCTGCCCG
GGCGATCACCTCTGCACCTTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC
 ^ ^
3217 HGIE2, 3229 NCOI,

LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu
3242 CTTCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCCTCGGAAGAAGCGGACGGTGGTCCCTC
GAAGGTGGAGGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG

ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer
3302 ACTGAATCAACCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC
TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG
 ^ ^
3332 SACI, 3346 HIND3,

SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly
3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCCGCCCTTCTGGC
AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG

CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro
3422 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCCTCCATGCCCCCCTGGAGGGGGAGCCT
ACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA
 ^
3437 EAM11051,

GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu
3482 GGGGATCCGGATCTTAGCGACGGGT CATGGTCAACGGTCAGTAGTGAGGCCAACGCGGAG
CCCCTAGGCCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGTTTGC GCCTC
 ^^ ^
3484 BAMHI, 3485 BSAB1, 3487 BSPE1,

AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla
3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC
CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGCGACGCGG

3589 DRA3, 3600 SAC2,

3602 AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn
GCGGAAGAACAGAACTGCCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT
CGCCTTCTTGTCTTTGACGGGTAGTTACGTGATTGTTGAGCAACGATGCAGTGGTGTTA
^ ^

3611 ALWN1, 3655 PFLM1,

3662 LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp
TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC
AACCACATAAGGTGGTGGAGTGCGTCACGAACGGTTTCCGTCTTCTTTCACTGTAAACTG
^

3681 DRA3,

3722 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla
AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG
TCTGACGTTCAAGACCTGTCGGTAATGGTCTGTCATGAGTTCTCCAATTTTCGTCGCCGC

3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis
TCAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGACGCTGACGCCCCACAC
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGGGGTGTG
^

3816 HIND3,

3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla
TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAGACGTCCGTTGCCATGCCAGAAAGGCC
AGTCGGTTTAGGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG
^ ^

3875 AAT2, 3890 BGLI,

3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp
GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCAATAGAC
CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGTTATCTG

3962 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys
ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGTTCGTAAG
TGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGACTCTTCCCCCAGCATTC

4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu
CCAGCTCGTCTCATCGTGTCCCCGATCTGGGCGTGCGCGTGTGCGAAAAGATGGCTTTG
GGTCGAGCAGAGTAGCACAAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC

4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr
TACGACGTGGTTACAAAGCTCCCTTGGCCGTGATGGGAAGCTCCTACGGATTCCAATAC
ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG

4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet
TCACCAGGACAGCGGGTTGAATTCCTCGTCAAGCGTGGAAGTCCAAGAAAACCCCAATG
AGTGGTCTGTGCGCCCACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTTGGGGTTAC
^

4160 ECORI,

4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr
GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG
CCCAAGAGCATACTATGGGCGACGAACTGAGGTGTCAGTGAAGTCTCGCTGTAGGCATGC
^ ^

00221154460

4229 DRD1, 4236 ALWN1,

4262 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer
GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCAAGCCCGGTGGCCATCAAGTCC
CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTTCGGGCGCACCGGTAGTTCAGG

4301 BGLI, 4308 BALI,

4322 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly
CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC
GAGTGGCTCTCCGAAATACAACCCCGGGAGAATGGTTAAGTTCCCCCTCTTGACGCCG

4345 APAI,

4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys
TATCGCAGGTGCCGCGGAGCGGCGTACTGACAACCTAGCTGTGGTAACACCCTCACTGTC
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTGTGGGAGTGAACG

4442 TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal
TACATCAAGGCCCGGGCAGCCTGTGAGCCGAGGGCTCCAGGACTGCACCATGCTCGTG
ATGTAGTTCCGGGCGCGTCCGACAGCTCGGCGTCCCGAGGTCTTGACGTGGTACGAGCAC

4452 SMAI XMAI,

4502 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer
TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGTCCAGGAGGACGCGCGGAGC
ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCCTCCTGCGCCGCTCG

4508 DRD1, 4511 TTH3I,

4562 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln
CTGAGAGCCTTCACGGAGGCTATGACCAGTACTCGCCCCCCTGGGGACCCCCACAA
GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGCGGGGGGGACCCCTGGGGGGTGT

4622 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp
CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTGAGTCCGCCACGAC
GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGTG

4637 SACI,

4682 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla
GGCGCTGGAAAGAGGGTCTACTACCTACCCGTGACCCTACAACCCCTCGCGAGAGCT
CCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGGAGCGCTCTCGA

4731 NRUI,

4742 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe
GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT
CGCACCTCTGTGTTCTGTGTGAGGTCAGTTAAGGACCGATCCGTTGTATTAGTACAAA

4802 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla
GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTTCTTTAGCGTCTTATAGCC
CGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG

4806 PFLM1, 4807 DRA3,

ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu

4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA
TCCCTGGTGAACCTTGTCCGGGAGCTAACGCTCTAGATGCCCCGGACGATGAGGTATCTT
^

4893 BGL2,

ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis
4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC
GGTGACCTAGATGGAGGTAGTAAGTTTCTGAGGTACCGGAGTTCGCGTAAAAGTGAGGTG
^

4954 NCOI,

SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro
4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACTGGGGTACCG
TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC
^

5015 SPHI, 5035 KPNI,

ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly
5042 CCCTTGGAGCTTGGAGACACCGGGCCCGGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA
GGGAACGCTCGAACCTCTGTGGCCCCGGCCTCGCAGGCGCGATCCGAAGACCGGTCTCCT
^

5064 APAI, 5091 BALI,

GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys
5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAA
CCGTCCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT
^

5113 NDEI,

LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr
5162 CTCCTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTTACGGCTGGCTAC
GAGTGAGGTTATCGCCGGCGACCGGTTCGACCTGAACAGGCCGACCAAGTGCCGACCGATG
^^ ^ ^

5174 NOTI, 5175 EAG1 XMA3, 5182 BALI, 5186 PVU2,

SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys
5222 AGCGGGGAGACATTTATCACAGCGTGTCTCATGCCGGCCCCGCTGGATCTGGTTTTGC
TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGGCCGGGGCGACCTAGACCAAACG
^

5240 DRA3,

LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn
5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCACGAAT
GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA
^

5295 PSTI,

ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe
5342 CCTAAACCTCAAAGAAAGACCAAACGTAACACCAACCGCGCGCCGAGGACGTCAAGTTC
GGATTTGGAGTTTCTTTCTGGTTTGCATTGTGGTTGGCCGCGCGCTCCTGCAGTTCAAG
^^ ^

5380 NOTI, 5381 EAG1 XMA3, 5390 AAT2, 5401 SMAI XMAI,

ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu
5402 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTGCGCGCAGGGGCCCTAGATTG
GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC
^

002247 544260

5724 HGIE2, 5755 SALI,

MetAlaAlaTyrAlaAlaGlnGlyTyrLysValLeuValLeuAsn
2 AGCTTACAAAACAAAATGGCTGCATATGCAGCTCAGGGCTATAAGGTGCTAGTACTCAAC
TCGAATGTTTTGTTTTACCGACGTATACGTCGAGTCCCGATATTCCACGATCATGAGTTG
1 HIND3, 24 NDEI, 52 SCAI,
ProSerValAlaAlaThrLeuGlyPheGlyAlaTyrMetSerLysAlaHisGlyIleAsp
62 CCCTCTGTTGCTGCAACACTGGGCTTTGGTGCTTACATGTCCAAGGCTCATGGGATCGAT
GGGAGACAACGACGTTGTGACCCGAAACCACGAATGTACAGGTTCCGAGTACCCTAGCTA
116 CLAI,
ProAsnIleArgThrGlyValArgThrIleThrThrGlySerProIleThrTyrSerThr
122 CCTAACATCAGGACCGGGGTGAGAACAATTACCACTGGCAGCCCCATCAGTACTCCACC
GGATTGTAGTCCTGGCCCCACTCTTGTTAATGGTGACCGTCGGGGTAGTGATGAGGTGG
TyrGlyLysPheLeuAlaAspGlyGlyCysSerGlyGlyAlaTyrAspIleIleIleCys
182 TACGGCAAGTTTCCTTGCCGACGGCGGGTGCTCGGGGGGCGCTTATGACATAATAATTTGT
ATGCCGTTCAAGGAACGGCTGCCGCCCCACGAGCCCCCGGAATACTGTATTATTAAACA
AspGluCysHisSerThrAspAlaThrSerIleLeuGlyIleGlyThrValLeuAspGln
242 GACGAGTGCCACTCCACGGATGCCACATCCATCTTGGGCATTGGCACTGTCCTTGACCAA
CTGCTCACGGTGAGGTGCCTACGGTGTAGGTAGAACCCGTAACCGTGACAGGAAGTGGTT
AlaGluThrAlaGlyAlaArgLeuValValLeuAlaThrAlaThrProProGlySerVal
302 GCAGAGACTGCGGGGGCGAGACTGGTTGTGCTCGCCACCGCCACCCCTCCGGGCTCCGTC
CGTCTCTGACGCCCCCGCTCTGACCAACACGAGCGGTGGCGGTGGGGAGGCCCGAGGCAG
303 ALWN1,
ThrValProHisProAsnIleGluGluValAlaLeuSerThrThrGlyGluIleProPhe
362 ACTGTGCCCCATCCCAACATCGAGGAGGTTGCTCTGTCCACCACCGGAGAGATCCCTTTT
TGACACGGGGTAGGGTTGTAGCTCCTCCAACGAGACAGGTGGTGGCCTCTCTAGGGAAAA
TyrGlyLysAlaIleProLeuGluValIleLysGlyGlyArgHisLeuIlePheCysHis
422 TACGGCAAGGCTATCCCCCTCGAAGTAATCAAGGGGGGAGACATCTCATCTTCTGTCAT
ATGCCGTTCCGATAGGGGGAGCTTCATTAGTTCCCCCCTCTGTAGAGTAGAAGACAGTA

0034450

SerLysLysLysCysAspGluLeuAlaAlaLysLeuValAlaLeuGlyIleAsnAlaVal
 482 TCAAAGAAGAAGTGCACGAACTCGCCGCAAAGCTGGTGCATTGGGCATCAATGCCGTG
 AGTTTCTTCTTCACGCTGCTTGAGCGGCGTTTCGACCAGCGTAACCCGTAGTTACGGCAC
 AlaTyrTyrArgGlyLeuAspValSerValIleProThrSerGlyAspValValValVal
 542 GCCTACTACCGCGGTCTTGACGTGTCCGTCATCCCACCAGCGGCGATGTTGTGTCGTCGTG
 CGGATGATGGCGCCAGAAGTGCACAGGCAGTAGGGCTGGTCGCCGCTACAACAGCAGCAC
 550 SAC2, 560 DRD1,
 AlaThrAspAlaLeuMetThrGlyTyrThrGlyAspPheAspSerValIleAspCysAsn
 602 GCAACCGATGCCCTCATGACCGGCTATACCGGCGACTTCGACTCGGTGATAGACTGCAAT
 CGTTGGCTACGGGAGTACTGGCCGATATGGCCGCTGAAGCTGAGCCACTATCTGACGTTA
 615 BSPH1,
 ThrCysValThrGlnThrValAspPheSerLeuAspProThrPheThrIleGluThrIle
 662 ACGTGTGTCAACCCAGACAGTTCGATTTACGCTTGACCTACCTTCACCATTGAGACAATC
 TGCACACAGTGGGTCTGTACGCTAAAGTCGGAAGTGGGATGGAAGTGGTAACTCTGTTAG
 ThrLeuProGlnAspAlaValSerArgThrGlnArgArgGlyArgThrGlyArgGlyLys
 722 ACGCTCCCCCAAGATGCTGTCTCCCGCACTCAACGTCGGGGCAGGACTGGCAGGGGGAAG
 TGCGAGGGGGTTCTACGACAGAGGGCGTGAGTTGCAGCCCGTCCTGACCGTCCCCCTTC
 ProGlyIleTyrArgPheValAlaProGlyGluArgProSerGlyMetPheAspSerSer
 782 CCAGGCATCTACAGATTGTGGCACCGGGGGAGCGCCCTCCGGCATGTTGCGACTCGTCC
 GGTCCGTAGATGTCTAAACACCGTGGCCCCCTCGCGGGGAGGCCGTACAAGCTGAGCAGG
 816 BGLI, 833 DRD1,
 ValLeuCysGluCysTyrAspAlaGlyCysAlaTrpTyrGluLeuThrProAlaGluThr
 842 GTCCTCTGTGAGTGCTATGACGCAGGCTGTGCTTGGTATGAGCTCACGCCCCGCCGAGACT
 CAGGAGACACTCACGATACTGCGTCCGACACGAACCATACTCGAGTGCGGGGCGGCTCTGA
 881 SACI,
 ThrValArgLeuArgAlaTyrMetAsnThrProGlyLeuProValCysGlnAspHisLeu
 902 ACAGTTAGGCTACGAGCGTACATGAACACCCCGGGGCTTCCCGTGTGCCAGGACCATCTT
 TGTCAATCCGATGCTCGCATGTACTTGTGGGGCCCCGAAGGGCACACGGTCCTGGTAGAA
 931 SMAI XMAI,
 GluPheTrpGluGlyValPheThrGlyLeuThrHisIleAspAlaHisPheLeuSerGln
 962 GAATTTTGGGAGGGCGTCTTTACAGGCCTCACTCATATAGATGCCCCTTTCTATCCCAG
 CTTAAAACCTCCCGCAGAAATGTCCGGAGTGAGTATATCTACGGGTGAAAGATAGGGTC
 985 STUI,
 ThrLysGlnSerGlyGluAsnLeuProTyrLeuValAlaTyrGlnAlaThrValCysAla
 1022 ACAAGCAGAGTGGGGAGAACCTTCCTTACCTGGTAGCGTACCAAGCCACCGTGTGCGCT
 TGTTTCGTCTACCCCTCTTGGAAGGAATGGACCATCGCATGGTTCGGTGGCACACGCGA
 1069 DRA3,
 ArgAlaGlnAlaProProProSerTrpAspGlnMetTrpLysCysLeuIleArgLeuLys
 1082 AGGGCTCAAGCCCCCTCCCCCATCGTGGGACCAGATGTGGAAGTGTGTTGATTGCGCTCAAG

Variable	Mean	SD	Min	Max	Skewness	Kurtosis	Normality
Age	35.2	12.5	18	65	0.15	3.2	0.98
Gender	1.2	0.4	1	2	0.05	3.0	0.99
Education	12.5	2.1	9	16	0.25	3.5	0.97
Income	1500	500	500	3000	0.35	3.8	0.96
Marital Status	1.8	0.4	1	2	0.05	3.0	0.99
Occupation	1.5	0.5	1	3	0.15	3.2	0.98
Health Status	1.2	0.4	1	2	0.05	3.0	0.99
Stress Level	2.5	1.0	1	4	0.25	3.5	0.97
Life Satisfaction	3.5	1.2	1	5	0.15	3.2	0.98
Resilience	2.8	0.8	1	4	0.15	3.2	0.98
Optimism	3.2	1.0	1	5	0.15	3.2	0.98
Emotional Stability	2.5	0.8	1	4	0.15	3.2	0.98
Self-Esteem	3.0	1.0	1	5	0.15	3.2	0.98
Life Purpose	2.8	0.8	1	4	0.15	3.2	0.98
Gratitude	3.5	1.2	1	5	0.15	3.2	0.98
Forgiveness	3.0	1.0	1	5	0.15	3.2	0.98
Resilience	2.8	0.8	1	4	0.15	3.2	0.98
Optimism	3.2	1.0	1	5	0.15	3.2	0.98
Emotional Stability	2.5	0.8	1	4	0.15	3.2	0.98
Self-Esteem	3.0	1.0	1	5	0.15	3.2	0.98
Life Purpose	2.8	0.8	1	4	0.15	3.2	0.98
Gratitude	3.5	1.2	1	5	0.15	3.2	0.98
Forgiveness	3.0	1.0	1	5	0.15	3.2	0.98
Resilience	2.8	0.8	1	4	0.15	3.2	0.98
Optimism	3.2	1.0	1	5	0.15	3.2	0.98
Emotional Stability	2.5	0.8	1	4	0.15	3.2	0.98
Self-Esteem	3.0	1.0	1	5	0.15	3.2	0.98
Life Purpose	2.8	0.8	1	4	0.15	3.2	0.98
Gratitude	3.5	1.2	1	5	0.15	3.2	0.98
Forgiveness	3.0	1.0	1	5	0.15	3.2	0.98
Resilience	2.8	0.8	1	4	0.15	3.2	0.98
Optimism	3.2	1.0	1	5	0.15	3.2	0.98
Emotional Stability	2.5	0.8	1	4	0.15	3.2	0.98
Self-Esteem	3.0	1.0	1	5	0.15	3.2	0.98
Life Purpose	2.8	0.8	1	4	0.15	3.2	0.98
Gratitude	3.5	1.2	1	5	0.15	3.2	0.98
Forgiveness	3.0	1.0	1	5	0.15	3.2	0.98
Resilience	2.8	0.8	1	4	0.15	3.2	0.98
Optimism	3.2	1.0	1	5	0.15	3.2	0.98
Emotional Stability	2.5	0.8	1	4	0.15	3.2	0.98
Self-Esteem	3.0	1.0	1	5	0.15	3.2	0.98
Life Purpose	2.8	0.8	1	4	0.15	3.2	0.98
Gratitude	3.5	1.2	1	5	0.15	3.2	0.98
Forgiveness	3.0	1.0	1	5	0.15	3.2	0.98
Resilience	2.8	0.8	1	4	0.15	3.2	0.98
Optimism	3.2	1.0	1	5	0.15	3.2	0.98
Emotional Stability	2.5	0.8	1	4	0.15	3.2	0.98
Self-Esteem	3.0	1.0	1	5	0.15	3.2	0.98
Life Purpose	2.8	0.8	1	4	0.15	3.2	0.98
Gratitude	3.5	1.2	1	5	0.15	3.2	0.98
Forgiveness	3.0	1.0	1	5	0.15	3.2	0.98
Resilience	2.8	0.8	1	4	0.15	3.2	0.98
Optimism	3.2						

ProThrLeuHisGlyProThrProLeuLeuTyrArgLeuGlyAlaValGlnAsnGluIle
1142 CCCACCCTCCATGGGCCAACCCCCTGCTATACAGACTGGGCGCTGTTCAGAATGAAATC
GGGTGGGAGGTACCCGGTTGTGGGGACGATATGTCTGACCCGCGACAAGTCTTACTTTAG

1202 ThrLeuThrHisProValThrLysTyrIleMetThrCysMetSerAlaAspLeuGluVal
ACCCTGACGCACCCAGTCACCAAATACATCATGACATGCATGTCGGCCGACCTGGAGGTC
TGGGACTGCGTGGGTCACTGGTTTATGTAGTACTGTACGTACAGCCGGCTGGACCTCCAG

ValThrSerThrTrpValLeuValGlyGlyValLeuAlaAlaLeuAlaAlaTyrCysLeu
1262 GTCACGAGCACCTGGGTGCTCGTTGGCGGCGTCCTGGCTGCTTTGGCCGCGTATTGCCTG
CAGTGCTCGTGGACCCACGAGCAACCGCCGAGGACCGACGAAACCGGCGCATAACGGAC

1322 SerThrGlyCysValValIleValGlyArgValValLeuSerGlyLysProAlaIleIle
TCAACAGGCTGCGTGGTCATAGTGGGCAGGGTCGTCTTGTCCGGGAAGCCGGCAATCATA
AGTTGTCCGACGCACCAGTATCACCCGTCCCAGCAGAACAGGCCCTTCGGCCGTTAGTAT

ProAspArgGluValLeuTyrArgGluPheAspGluMetGluGluCysSerGlnHisLeu
1382 CCTGACAGGGAAGTCCTCTACCGAGAGTTCGATGAGATGGAAGAGTGCTCTCAGCACTTA
GGACTGTCCCTTCAGGAGATGGCTCTCAAGCTACTCTACCTTCTCACGAGAGTCGTGAAT

ProTyrIleGluGlnGlyMetMetLeuAlaGluGlnPheLysGlnLysAlaLeuGlyLeu
1442 CCGTACATCGAGCAAGGGATGATGCTCGCCGAGCAGTTCAAGCAGAAGGCCCTCGGCCTC
GGCATGTAGCTCGTTCCCTACTACGAGCGGCTCGTCAAGTTCGTCTTCCGGGAGCCGGAG

1502 LeuGlnThrAlaSerArgGlnAlaGluValIleAlaProAlaValGlnThrAsnTrpGln
CTGCAGACCGCGTCCCGTCAGGCAGAGGTTATCGCCCCGTGCTGTCCAGACCAACTGGCAA
GACGCTCTGGCGCAGGGCAGTCCGCTCCAATAGCGGGGACGACAGGTCTGGTTGACCGTT

1562 LysLeuGluThrPheTrpAlaLysHisMetTrpAsnPheIleSerGlyIleGlnTyrLeu
AAACTCGAGACCTTCTGGGCGAAGCATATGTGGAACCTTCATCAGTGGGATACAATACTTG
TTTGAGCTCTGGAAGACCCGCTTCGTATACACCTTGAAGTAGTCACCCATGTTATGAAC

AlaGlyLeuSerThrLeuProGlyAsnProAlaIleAlaSerLeuMetAlaPheThrAla
1622 GCGGGCTTGTC AACGCTGCCTGGTAACCCCGCCATTGCTTCATTGATGGCTTTTACAGCT
CGCCCCGAACAGTTGCGACGGACCATTGGGGCGGTAACGAAGTAAC TACCGAAAATGTCGA

AlaValThrSerProLeuThrThrSerGlnThrLeuLeuPheAsnIleLeuGlyGlyTrp
1682 GCTGTCAACAGCCCACTAACCCTAGCCAAACCCTCCTCTTCAACATATTGGGGGGGTGG
CGACAGTGGTCGGGTGATTGGTGATCGGTTTGGGAGGAGAAGTTGTATAACCCCCCACC

[illegible]

ValAlaAlaGlnLeuAlaAlaProGlyAlaAlaThrAlaPheValGlyAlaGlyLeuAla
1742 GTGGCTGCCAGCTCGCCGCCCCCGGTGCCGCTACTGCCTTTGTGGGCGCTGGCTTAGCT
CACCGACGGGTCGAGCGGCGGGGGCCACGGCGATGACGGAAACACCCGCGACCGAATCGA
1794 ESP1,
GlyAlaAlaIleGlySerValGlyLeuGlyLysValLeuIleAspIleLeuAlaGlyTyr
1802 GGCGCCGCCATCGGCAGTGTGGACTGGGGAAGGTCCTCATAGACATCCTTGCAGGGTAT
CCGCGGCGGTAGCCGTCACAACCTGACCCCTTCCAGGAGTATCTGTAGGAACGTCCCATA
1802 KAS1 NARI,
GlyAlaGlyValAlaGlyAlaLeuValAlaPheLysIleMetSerGlyGluValProSer
1862 GGCGCGGGCGTGGCGGGAGCTCTTGTGGCATTCAAGATCATGAGCGGTGAGGTCCCCTCC
CCGCGCCCGCACCGCCCTCGAGAACACCGTAAGTTCTAGTACTCGCCACTCCAGGGGAGG
1878 SACI, 1899 BSPH1,
ThrGluAspLeuValAsnLeuLeuProAlaIleLeuSerProGlyAlaLeuValValGly
1922 ACGGAGGACCTGGTCAATCTACTGCCCGCCATCCTCTCGCCCGGAGCCCTCGTAGTCGGC
TGCCTCCTGGACCAGTTAGATGACGGGCGGTAGGAGAGCGGGCCTCGGGAGCATCAGCCG
1928 TTH3I,
ValValCysAlaAlaIleLeuArgArgHisValGlyProGlyGluGlyAlaValGlnTrp
1982 GTGGTCTGTGCAGCAATACTGCGCCGGCACGTTGGCCCGGGCGAGGGGGCAGTGCAGTGG
CACCAGACACGTCGTTATGACGCGGCCGTGCAACCGGGCCCGCTCCCCCGTCACGTCACC
2004 NAEI, 2017 SMAI XMAI,
MetAsnArgLeuIleAlaPheAlaSerArgGlyAsnHisValSerProThrHisTyrVal
2042 ATGAACCGGCTGATAGCCTTCGCCTCCCGGGGAACCATGTTCCCCCACGCACTACGTG
TACTTGGCCGACTATCGGAAGCGGAGGGCCCCCTTGGTACAAAGGGGGTGCGTGATGCAC
2067 SMAI XMAI, 2093 DRA3,
ProGluSerAspAlaAlaAlaArgValThrAlaIleLeuSerSerLeuThrValThrGln
2102 CCGGAGAGCGATGCAGCTGCCCGCGTCACTGCCATACTCAGCAGCCTCACTGTAACCCAG
GGCCTCTCGCTACGTCGACGGGCGCAGTGACGGTATGAGTCGTCGGAGTGACATTGGGTC
2115 PVU2, 2159 ALWN1,
LeuLeuArgArgLeuHisGlnTrpIleSerSerGluCysThrThrProCysSerGlySer
2162 CTCCTGAGGCGACTGCACCACTGGATAAGCTCGGAGTGTACCACTCCATGCTCCGGTTCC
GAGGACTCCGCTGACGTGGTCACCTATTCGAGCCTCACATGGTGAGGTACGAGGCCAAGG
2164 MST2, 2220 ECON1,
TrpLeuArgAspIleTrpAspTrpIleCysGluValLeuSerAspPheLysThrTrpLeu
2222 TGGCTAAGGGACATCTGGGACTGGATATGCGAGGTGTTGAGCGACTTTAAGACCTGGCTA
ACCGATTCCCTGTAGACCTGACCTATACGCTCCACAACCTCGGTGAAATTCTGGACCGAT
2282 LysAlaLysLeuMetProGlnLeuProGlyIleProPheValSerCysGlnArgGlyTyr
AAAGCTAAGCTCATGCCACAGCTGCCTGGGATCCCCTTTGTGTCCTGCCAGCGCGGGTAT
TTTCGATTTCGAGTACGGTGTGACGCGACCCTAGGGGAAACACAGGACGGTCGCGCCCAT
2285 ESP1, 2300 PVU2, 2310 BAMHI,

2342 LysGlyValTrpArgGlyAspGlyIleMetHisThrArgCysHisCysGlyAlaGluIle
 AAGGGGGTCTGGCGAGGGGACGGCATCATGCACACTCGCTGCCACTGTGGAGCTGAGATC
 TTCCCCAGACCGCTCCCCTGCCGTAGTACGTGTGAGCGACGGTGACACCTCGACTCTAG

 2402 ThrGlyHisValLysAsnGlyThrMetArgIleValGlyProArgThrCysArgAsnMet
 ACTGGACATGTCAAAAACGGGACGATGAGGATCGTCGGTCCTAGGACCTGCAGGAACATG
 TGACCTGTACAGTTTTTGCCTGCTACTCCTAGCAGCCAGGATCCTGGACGTCTTGATAC
 ^ ^ ^
 2425 BSAB1, 2441 AVR2, 2448 SSE83871, 2449 PSTI,

 2462 TrpSerGlyThrPheProIleAsnAlaTyrThrThrGlyProCysThrProLeuProAla
 TGGAGTGGGACCTTCCCCATTAATGCCTACACCACGGGCCCTGTACCCCTTCCTGCG
 ACCTCACCTGGAAGGGTAATTACGGATGTGGTGCCCGGGACATGGGGGAAGGACGC
 ^ ^
 2480 ASE1, 2497 APAI,

 2522 ProAsnTyrThrPheAlaLeuTrpArgValSerAlaGluGluTyrValGluIleArgGln
 CCGAAGTACACGTTTCGCGCTATGGAGGGTGTCTGCAGAGGAATACGTGGAGATAAGGCAG
 GGCTTGATGTGCAAGCGGATACCTCCACAGACGTCTCCTTATGCACCTCTATTCCGTC
 ^
 2553 PSTI,

 2582 ValGlyAspPheHisTyrValThrGlyMetThrThrAspAsnLeuLysCysProCysGln
 GTGGGGGACTTCCACTACGTGACGGGTATGACTACTGACAATCTTAAATGCCCGTGCCAG
 CACCCCTGAAGGTGATGCACTGCCCATACTGATGACTGTTAGAATTTACGGGCACGGTC
 ^
 2594 DRA3,

 2642 ValProSerProGluPhePheThrGluLeuAspGlyValArgLeuHisArgPheAlaPro
 GTCCCATCGCCGAATTTTTACAGAATTGGACGGGGTGGCGCTACATAGGTTTGGCCCC
 CAGGGTAGCGGGCTTAAAAAGTGTCTTAACCTGCCCCACGGGATGTATCAAACGCGGG

 2702 ProCysLysProLeuLeuArgGluGluValSerPheArgValGlyLeuHisGluTyrPro
 CCTGCAAGCCCTTGCTGCGGGAGGAGGTATCATTACAGAGTAGGACTCCACGAATACCCG
 GGGACGTTGCGGAACGACGCCCTCCTCCATAGTAAGTCTCATCTGAGGTGCTTATGGGC
 ^
 2757 HGIE2,

 2762 ValGlySerGlnLeuProCysGluProGluProAspValAlaValLeuThrSerMetLeu
 GTAGGGTCGCAATTACCTTGCGAGCCCGAACCGGACGTGGCCGTGTTGACGTCCATGCTC
 CATCCAGCGTTAATGGAACGCTCGGGCTTGGCCTGCACCGGCACAACTGCAGGTACGAG
 ^
 2809 AAT2,

 2822 ThrAspProSerHisIleThrAlaGluAlaAlaGlyArgArgLeuAlaArgGlySerPro
 ACTGATCCCTCCCATATAACAGCAGAGGCGGGCGGCGAAGGTTGGCGAGGGGATCACCC
 TGACTAGGGAGGGTATATTGTCGTCTCCGCCGGCCCGCTTCCAACCGCTCCCCTAGTGGG
 ^
 2850 EAG1 XMA3,

 2882 ProSerValAlaSerSerSerAlaSerGlnLeuSerAlaProSerLeuLysAlaThrCys
 CCCTCTGTGGCCAGCTCCTCGGCTAGCCAGCTATCCGCTCCATCTCTCAAGGCAACTTGC
 GGGAGACACCGGTGAGGAGCCGATCGGTCGATAGGCGAGGTAGAGAGTTCCGTTGAACG
 ^ ^
 2889 BALI, 2903 NHEI,

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2942 ThrAlaAsnHisAspSerProAspAlaGluLeuIleGluAlaAsnLeuLeuTrpArgGln
 ACCGTAACCATGACTCCCCTGATGCTGAGCTCATAGAGGCCAACCTCCTATGGAGGCAG
 TGGCGATTGGTACTGAGGGGACTACGACTCGAGTATCTCCGTTGGAGGATACCTCCGTC
 ^ ^
 2966 ESP1, 2969 SACI,
 GluMetGlyGlyAsnIleThrArgValGluSerGluAsnLysValValIleLeuAspSer
 3002 GAGATGGGCGGCAACATCACCAGGGTTGAGTCAGAAAACAAAGTGGTGATTCTGGACTCC
 CTCTACCCGCCGTTGTAGTGGTCCCAACTCAGTCTTTTGTTCACCACTAAGACCTGAGG
 PheAspProLeuValAlaGluGluAspGluArgGluIleSerValProAlaGluIleLeu
 3062 TTCGATCCGCTTGTGGCGGAGGAGGACGAGCGGAGATCTCCGTACCCGCAGAAATCCTG
 AAGCTAGGCGAACACCGCCTCCTCCTGCTCGCCCTCTAGAGGCATGGGCGTCTTTAGGAC
 ^
 3096 BGL2,
 ArgLysSerArgArgPheAlaGlnAlaLeuProValTrpAlaArgProAspTyrAsnPro
 3122 CGGAAGTCTCGGAGATTCGCCCAGGCCCTGCCGTTTGGGCGCGCCGGACTATAACCCC
 GCCTTCAGAGCCTTAAGCGGGTCCGGGACGGGCAAACCCGCGCCGCCTGATATTGGGG
 ^ ^
 3143 ALWN1, 3164 EAG1 XMA3,
 ProLeuValGluThrTrpLysLysProAspTyrGluProProValValHisGlyCysPro
 3182 CCGCTAGTGGAGACGTGGAAAAAGCCCCACTACGAACCACCTGTGGTCCATGGCTGCCCG
 GGCGATCACCTCTGCACCTTTTTCGGGCTGATGCTTGGTGGACACCAGGTACCGACGGGC
 ^ ^
 3217 HGIE2, 3229 NCOI,
 LeuProProProLysSerProProValProProProArgLysLysArgThrValValLeu
 3242 CTTCCACCTCCAAAGTCCCCTCCTGTGCCTCCGCCTCGGAAGAAGCGGACGGTGGTCCCTC
 GAAGGTGGAGTTTCAGGGGAGGACACGGAGGCGGAGCCTTCTTCGCCTGCCACCAGGAG
 ThrGluSerThrLeuSerThrAlaLeuAlaGluLeuAlaThrArgSerPheGlySerSer
 3302 ACTGAATCAACCCTATCTACTGCCTTGGCCGAGCTCGCCACCAGAAGCTTTGGCAGCTCC
 TGACTTAGTTGGGATAGATGACGGAACCGGCTCGAGCGGTGGTCTTCGAAACCGTCGAGG
 ^ ^
 3332 SACI, 3346 HIND3,
 SerThrSerGlyIleThrGlyAspAsnThrThrThrSerSerGluProAlaProSerGly
 3362 TCAACTTCCGGCATTACGGGCGACAATACGACAACATCCTCTGAGCCCGCCCTTCTGGC
 AGTTGAAGGCCGTAATGCCCGCTGTTATGCTGTTGTAGGAGACTCGGGCGGGGAAGACCG
 CysProProAspSerAspAlaGluSerTyrSerSerMetProProLeuGluGlyGluPro
 3422 TGCCCCCCCCGACTCCGACGCTGAGTCCTATTCTCCATGCCCCCCTGGAGGGGGAGCCT
 ACGGGGGGGCTGAGGCTGCGACTCAGGATAAGGAGGTACGGGGGGGACCTCCCCCTCGGA
 ^
 3437 EAM11051,
 GlyAspProAspLeuSerAspGlySerTrpSerThrValSerSerGluAlaAsnAlaGlu
 3482 GGGGATCCGGATCTTAGCGACGGGTCAATGCTCAACGGTCAGTAGTGAGGCCAACGCGGAG
 CCCCTAGGCCCTAGAATCGCTGCCAGTACCAGTTGCCAGTCATCACTCCGGTTGCGCCTC
 ^ ^ ^
 3484 BAMHI, 3485 BSAB1, 3487 BSPE1,
 AspValValCysCysSerMetSerTyrSerTrpThrGlyAlaLeuValThrProCysAla
 3542 GATGTCGTGTGCTGCTCAATGTCTTACTCTTGGACAGGCGCACTCGTCACCCCGTGCGCC
 CTACAGCACACGACGAGTTACAGAATGAGAACCTGTCCGCGTGAGCAGTGGGGCACGCGG

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FIGURE 22 - Page 7

3589 DRA3, 3600 SAC2,

3602 AlaGluGluGlnLysLeuProIleAsnAlaLeuSerAsnSerLeuLeuArgHisHisAsn
GCGGAAGAACAGAACTGCCCATCAATGCACTAAGCAACTCGTTGCTACGTCACCACAAT
CGCCTTCTTGCTTTGACGGGTAGTTACGTGATTCGTTGAGCAACGATGCAGTGGTGTTA

3611 ALWN1, 3655 PFLM1,

3662 LeuValTyrSerThrThrSerArgSerAlaCysGlnArgGlnLysLysValThrPheAsp
TTGGTGTATTCCACCACCTCACGCAGTGCTTGCCAAAGGCAGAAGAAAGTCACATTTGAC
AACCACATAAGGTGGTGGAGTCCGTCACGAACGGTTTCCGTCTTCTTTCAGTGTAAGTGC

3681 DRA3,

3722 ArgLeuGlnValLeuAspSerHisTyrGlnAspValLeuLysGluValLysAlaAlaAla
AGACTGCAAGTTCTGGACAGCCATTACCAGGACGTACTCAAGGAGGTTAAAGCAGCGGCG
TCTGACGTTCAAGACCTGTCGGTAATGGTCCTGCATGAGTTCCTCAATTTTCGTCGCCCGC

3782 SerLysValLysAlaAsnLeuLeuSerValGluGluAlaCysSerLeuThrProProHis
TCAAAAGTGAAGGCTAACTTGCTATCCGTAGAGGAAGCTTGACAGCCTGACGCCCCACAC
AGTTTTCACTTCCGATTGAACGATAGGCATCTCCTTCGAACGTCGGACTGCGGGGGTGTG

3816 HIND3,

3842 SerAlaLysSerLysPheGlyTyrGlyAlaLysAspValArgCysHisAlaArgLysAla
TCAGCCAAATCCAAGTTTGGTTATGGGGCAAAAGACGTCCGTTGCCATGCCAGAAAGGCC
AGTCGGTTTGTAGTTCAAACCAATACCCCGTTTTCTGCAGGCAACGGTACGGTCTTTCCGG

3875 AAT2, 3890 BGLI,

3902 ValThrHisIleAsnSerValTrpLysAspLeuLeuGluAspAsnValThrProIleAsp
GTAACCCACATCAACTCCGTGTGGAAAGACCTTCTGGAAGACAATGTAACACCAATAGAC
CATTGGGTGTAGTTGAGGCACACCTTTCTGGAAGACCTTCTGTTACATTGTGGTTATCTG

3962 ThrThrIleMetAlaLysAsnGluValPheCysValGlnProGluLysGlyGlyArgLys
ACTACCATCATGGCTAAGAACGAGGTTTTCTGCGTTTCAGCCTGAGAAGGGGGTTCGTAAG
TGATGGTAGTACCGATTCTTGCTCCAAAAGACGCAAGTCGGACTCTTCCCCCAGCATTC

4022 ProAlaArgLeuIleValPheProAspLeuGlyValArgValCysGluLysMetAlaLeu
CCAGCTCGTCTCATCGTGTCCCCGATCTGGGCGTGCGCGTGTGCGAAAAGATGGCTTTG
GGTCGAGCAGAGTAGCACAAGGGGCTAGACCCGCACGCGCACACGCTTTTCTACCGAAAC

4082 TyrAspValValThrLysLeuProLeuAlaValMetGlySerSerTyrGlyPheGlnTyr
TACGACGTGGTTACAAAGCTCCCCCTTGCCCGTGATGGGAAGCTCCTACGGATTCCAATAC
ATGCTGCACCAATGTTTCGAGGGGAACCGGCACTACCCTTCGAGGATGCCTAAGGTTATG

4142 SerProGlyGlnArgValGluPheLeuValGlnAlaTrpLysSerLysLysThrProMet
TCACCAGGACAGCGGGTTGAATTCCTCGTGCAAGCGTGGAAGTCCAAGAAAACCCCAATG
AGTGGTCTGTGCGCCCACTTAAGGAGCACGTTTCGCACCTTCAGGTTCTTTGGGGTTAC

4160 ECORI,

4202 GlyPheSerTyrAspThrArgCysPheAspSerThrValThrGluSerAspIleArgThr
GGGTTCTCGTATGATACCCGCTGCTTTGACTCCACAGTCACTGAGAGCGACATCCGTACG
CCCAAGAGCATACTATGGGCGACGAAACTGAGGTGTCAGTGACTCTCGCTGTAGGCATGC

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4229 DRD1, 4236 ALWN1,

4262 GluGluAlaIleTyrGlnCysCysAspLeuAspProGlnAlaArgValAlaIleLysSer
GAGGAGGCAATCTACCAATGTTGTGACCTCGACCCCAAGCCCGCTGGCCATCAAGTCC
CTCCTCCGTTAGATGGTTACAACACTGGAGCTGGGGGTTCTGGGCGCACCGGTAGTTCAGG

4301 BGLI, 4308 BALI,

4322 LeuThrGluArgLeuTyrValGlyGlyProLeuThrAsnSerArgGlyGluAsnCysGly
CTCACCGAGAGGCTTTATGTTGGGGGCCCTCTTACCAATTCAAGGGGGGAGAACTGCGGC
GAGTGGCTCTCCGAAATACAACCCCGGGAGAATGGTTAAGTTCCTCCCTCTTGACGCCG

4345 APAI,

4382 TyrArgArgCysArgAlaSerGlyValLeuThrThrSerCysGlyAsnThrLeuThrCys
TATCGCAGGTGCCGCGGAGCGGCGTACTGACAACCTAGCTGTGGTAACACCCCTCACTTGC
ATAGCGTCCACGGCGCGCTCGCCGCATGACTGTTGATCGACACCATTTGTTGGGAGTGAACG

4442 TyrIleLysAlaArgAlaAlaCysArgAlaAlaGlyLeuGlnAspCysThrMetLeuVal
TACATCAAGGCCCGGCGAGCCTGTGAGCCGCGAGGCTCCAGGACTGCACCATGCTCGTG
ATGTAGTTCCGGGCCCGTCCGACAGCTCGGCGTCCCGAGGTCCTGACGTGGTACGAGCAC

4452 SMAI XMAI,

4502 CysGlyAspAspLeuValValIleCysGluSerAlaGlyValGlnGluAspAlaAlaSer
TGTGGCGACGACTTAGTCGTTATCTGTGAAAGCGCGGGGGTCCAGGAGGACGCGCGGAGC
ACACCGCTGCTGAATCAGCAATAGACACTTTCGCGCCCCCAGGTCTCTCGCGCGCTCG

4508 DRD1, 4511 TTH3I,

4562 LeuArgAlaPheThrGluAlaMetThrArgTyrSerAlaProProGlyAspProProGln
CTGAGAGCCTTCACGGAGGCTATGACCAGGTACTCCGCCCCCCTGGGGACCCCCACAA
GACTCTCGGAAGTGCCTCCGATACTGGTCCATGAGGCGGGGGGACCCCTGGGGGTGTT

4622 ProGluTyrAspLeuGluLeuIleThrSerCysSerSerAsnValSerValAlaHisAsp
CCAGAATACGACTTGGAGCTCATAACATCATGCTCCTCCAACGTGTCACTCGCCACGAC
GGTCTTATGCTGAACCTCGAGTATTGTAGTACGAGGAGGTTGCACAGTCAGCGGGTGCTG

4637 SACI,

4682 GlyAlaGlyLysArgValTyrTyrLeuThrArgAspProThrThrProLeuAlaArgAla
GGCGCTGGAAAGAGGGTCTACTACCTCACCCGTGACCCTACAACCCCTCGCGAGAGCT
CCGCGACCTTTCTCCAGATGATGGAGTGGGCACTGGGATGTTGGGGGAGCGCTCTCGA

4731 NRUI,

4742 AlaTrpGluThrAlaArgHisThrProValAsnSerTrpLeuGlyAsnIleIleMetPhe
GCGTGGGAGACAGCAAGACACACTCCAGTCAATTCCTGGCTAGGCAACATAATCATGTTT
CGCACCTCTGTCGTTCTGTGTGAGGTCAAGTAAGGACCGATCCGTTGTATTAGTACAAA

4802 AlaProThrLeuTrpAlaArgMetIleLeuMetThrHisPhePheSerValLeuIleAla
GCCCCACACTGTGGGCGAGGATGATACTGATGACCCATTTCTTTAGCGTCTTATAGCC
CGGGGTGTGACACCCGCTCCTACTATGACTACTGGGTAAAGAAATCGCAGGAATATCGG

4806 PFLM1, 4807 DRA3,

ArgAspGlnLeuGluGlnAlaLeuAspCysGluIleTyrGlyAlaCysTyrSerIleGlu

00227 527260

4862 AGGGACCAGCTTGAACAGGCCCTCGATTGCGAGATCTACGGGGCCTGCTACTCCATAGAA
 TCCCTGGTCCGAACCTTGTCCGGGAGCTAACGCTCTAGATGCCCCGGACGATGAGGTATCTT
 ^
 4893 BGL2,
 ProLeuAspLeuProProIleIleGlnArgLeuHisGlyLeuSerAlaPheSerLeuHis
 4922 CCACTGGATCTACCTCCAATCATTCAAAGACTCCATGGCCTCAGCGCATTTTCACTCCAC
 GGTGACCTAGATGGAGGTTAGTAAGTTTCTGAGGTACCGGAGTCGCGTAAAAGTGAGGTG
 ^
 4954 NCOI,
 SerTyrSerProGlyGluIleAsnArgValAlaAlaCysLeuArgLysLeuGlyValPro
 4982 AGTTACTCTCCAGGTGAAATCAATAGGGTGGCCGCATGCCTCAGAAAACCTGGGGTACCG
 TCAATGAGAGGTCCACTTTAGTTATCCACCGGCGTACGGAGTCTTTTGAACCCCATGGC
 ^
 5015 SPHI, 5035 KPNI,
 ProLeuArgAlaTrpArgHisArgAlaArgSerValArgAlaArgLeuLeuAlaArgGly
 5042 CCCTTGCGAGCTTGGAGACACCGGGCCCGAGCGTCCGCGCTAGGCTTCTGGCCAGAGGA
 GGAACGCTCGAACCTCTGTGGCCCCGGGCTCGCAGGCGCGATCCGAAGACCGGTCTCCT
 ^
 5064 APAI, 5091 BALI,
 GlyArgAlaAlaIleCysGlyLysTyrLeuPheAsnTrpAlaValArgThrLysLeuLys
 5102 GGCAGGGCTGCCATATGTGGCAAGTACCTCTTCAACTGGGCAGTAAGAACAAAGCTCAAA
 CCGTCCCCGACGGTATACACCGTTCATGGAGAAGTTGACCCGTCATTCTTGTTCGAGTTT
 ^
 5113 NDEI,
 LeuThrProIleAlaAlaAlaGlyGlnLeuAspLeuSerGlyTrpPheThrAlaGlyTyr
 5162 CTACTCCAATAGCGGCCGCTGGCCAGCTGGACTTGTCCGGCTGGTTCACGGCTGGCTAC
 GAGTGAGGTTATCGCCGGCGACCGGTGACCTGAACAGGCGGACCAAGTGCCGACCGATG
 ^ ^ ^ ^
 5174 NOTI, 5175 EAGI XMA3, 5182 BALI, 5186 PVU2,
 SerGlyGlyAspIleTyrHisSerValSerHisAlaArgProArgTrpIleTrpPheCys
 5222 AGCGGGGGAGACATTTATCACAGCGTGTCTCATGCCCCGGCCCCGCTGGATCTGGTTTTGC
 TCGCCCCCTCTGTAAATAGTGTGCGACAGAGTACGGGCCGGGGCGACCTAGACCAAAACG
 ^
 5240 DRA3,
 LeuLeuLeuLeuAlaAlaGlyValGlyIleTyrLeuLeuProAsnArgMetSerThrAsn
 5282 CTACTCCTGCTTGCTGCAGGGGTAGGCATCTACCTCCTCCCCAACCGAATGAGCACGAAT
 GATGAGGACGAACGACGTCCCCATCCGTAGATGGAGGAGGGGTGGCTTACTCGTGCTTA
 ^
 5295 PSTI,
 ProLysProGlnArgLysThrLysArgAsnThrAsnArgArgProGlnAspValLysPhe
 5342 CCTAAACCTCAAAGAAAGACCAACGTAACACCAACCGGCGGCCGAGGACGTCAAGTTC
 GGATTTGGAGTTTCTTTCTGGTTTGCATTGTGGTTGGCCCGCGGCGTCTGCAGTTCAAG
 ^ ^ ^
 5380 NOTI, 5381 EAGI XMA3, 5390 AAT2, 5401 SMAI XMAI,
 ProGlyGlyGlyGlnIleValGlyGlyValTyrLeuLeuProArgArgGlyProArgLeu
 5402 CCGGGTGGCGGTGAGATCGTTGGTGGAGTTTACTTGTGCGCGCAGGGGGCCTAGATTG
 GGCCACCGCCAGTCTAGCAACCACCTCAAATGAACAACGGCGCGTCCCCGGGATCTAAC
 ^

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FIGURE 22 - Page 10

5449 APAI,

GlyValArgAlaThrArgLysThrSerGluArgSerGlnProArgGlyArgArgGlnPro
5462 GGTGTGCGCGCGACGAGAAAGACTTCCGAGCGGTCGCAACCTCGAGGTAGACGTCAGCCT
CCACACGCGCGCTGCTCTTTCTGAAGGCTCGCCAGCGTTGGAGCTCCATCTGCAGTCGGA

5467 BSSH2, 5478 XMNI, 5502 XHOI, 5511 AAT2,

IleProLysAlaArgArgProGluGlyArgThrTrpAlaGlnProGlyTyrProTrpPro
5522 ATCCCAAGGCTCGTCGGCCCGAGGGCAGGACCTGGGCTCAGCCCGGGTACCCTTGGCCC
TAGGGGTTCCGAGCAGCCGGGCTCCCGTCCTGGACCCGAGTCGGGCCCATGGGAACCGGG

5548 ALWN1, 5558 ESP1, 5564 SMAI XMAI, 5568 KPNI,

LeuTyrGlyAsnGluGlyCysGlyTrpAlaGlyTrpLeuLeuSerProArgGlySerArg
5582 CTCTATGGCAATGAGGGCTGCGGGTGGGCGGGATGGCTCCTGTCTCCCGTGGCTCTCGG
GAGATACCGTTACTCCCGACGCCACCCGCCCTACCGAGGACAGAGGGGCACCGAGAGCC

ProSerTrpGlyProThrAspProArgArgArgSerArgAsnLeuGlyLysValIleAsp
5642 CCTAGCTGGGGCCCCACAGACCCCGGCGTAGGTCGCGCAATTTGGGTAAGGTCATCGAT
GGATCGACCCCGGGGTGTCTGGGGGCCGCATCCAGCGCGTTAAACCCATTCCAGTAGCTA

5650 APAI, 5696 CLAI,

ThrLeuThrCysGlyPheAlaAspLeuMetGlyTyrIleProLeuValGlyAlaProLeu
5702 ACCCTTACGTGCGGCTTCGCCGACCTCATGGGGTACATACCGCTCGTCGGCGCCCCTCTT
TGGGAATGCACGCCGAAGCGGCTGGAGTACCCCATGTATGGCGAGCAGCCGCGGGGAGAA

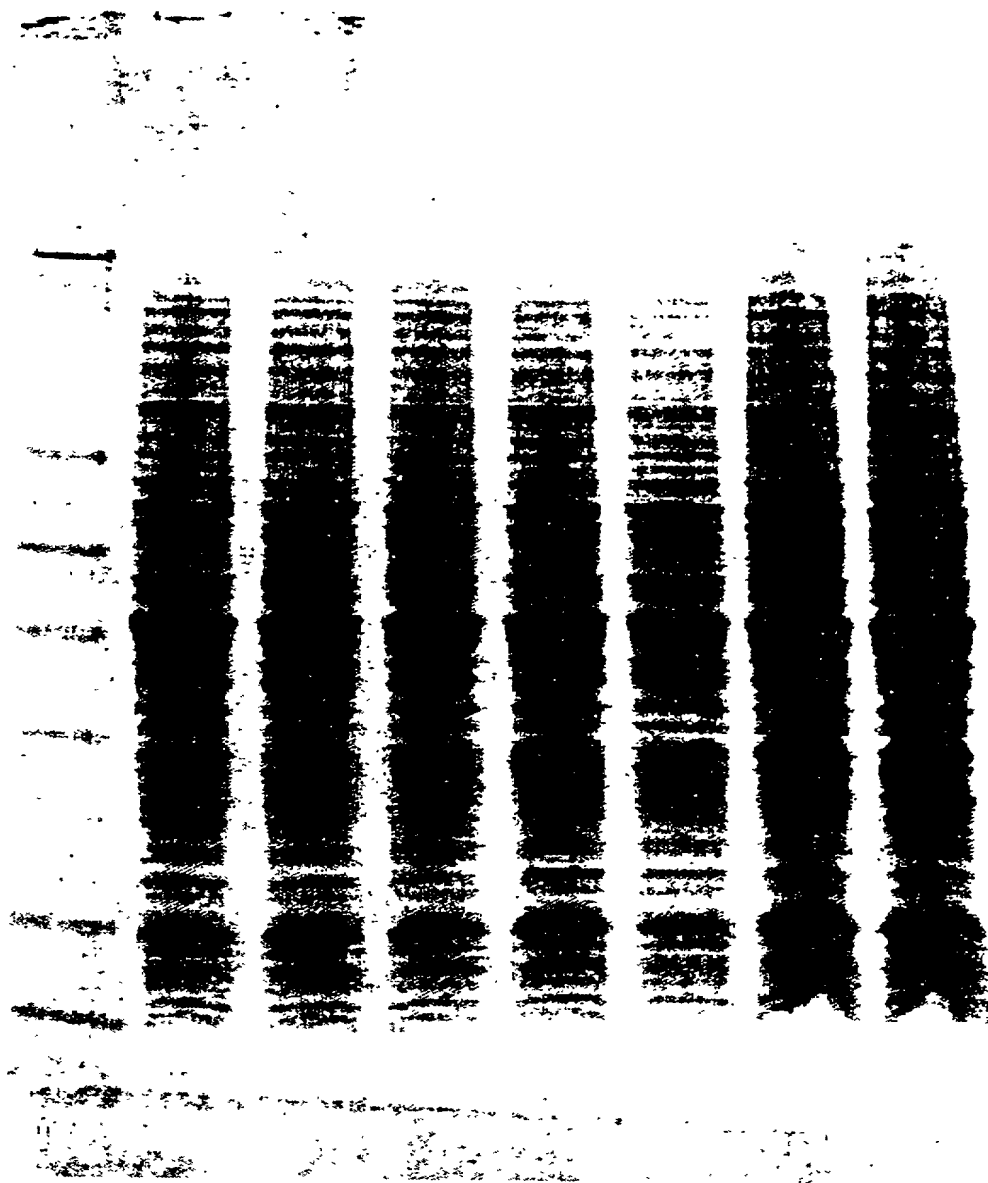
5724 HGIE2, 5750 KAS1 NARI, 5756 ECON1,

GlyGlyAlaAlaArgAlaOC AM
5762 GGAGGCGCTGCCAGGGCCTAATAGTCGAC
CCTCCGCGACGGTCCCGGATTATCAGCTG

5785 SALI,

0022T 524260

FIGURE 23



002211 524260

COMBINED DECLARATION AND POWER OF ATTORNEY
FOR UTILITY PATENT APPLICATION

AS A BELOW-NAMED INVENTOR, I HEREBY DECLARE THAT:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: NOVEL HCV NON-STRUCTURAL POLYPEPTIDE the specification of which

 X is attached hereto
 was filed on

and assigned Serial No.

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

I acknowledge and understand that I am an individual who has a duty to disclose information which is material to the patentability of the claims of this application in accordance with Title 37, Code of Federal Regulations, §§ 1.56(a) and (b) which state:

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated

through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office,

or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

I do not know and do not believe this invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application. This invention was not in public use or on sale in the United States of America more than one year prior to this application. This invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than six months prior to this application.

I hereby claim priority benefits under Title 35, United States Code § 119(e)(1) of any United States provisional application(s) for patent as indicated below and have also identified below any application for patent on this invention having a filing date before that of the application for patent on which priority is claimed:

<u>Application No.</u>	<u>Date of Filing (day/month/year)</u>	<u>Priority Claimed</u>
60/167,502	24 November 1999	Yes <u>X</u> No <u> </u>

I hereby appoint the following attorneys and agents to prosecute that application and to transact all business in the Patent and Trademark Office connected therewith and to file, to prosecute and to transact all business in connection with all patent applications directed to the invention:

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This appointment, including the right to delegate this appointment, shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signature: _____

Date _____

Full Name of Inventor: Doris COIT

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Date _____

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Signature: _____

Date _____

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Atty Dkt No. PP01617.002
PATENT

"Express Mail" Mailing Label No. EL 668 933 832 US
Date of Deposit November 22, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

PATRICIA K. HIMENES
Typed or Printed Name of Person Mailing Paper or Fee

Patricia K. Himenes
Signature of Person Mailing Paper or Fee

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

COIT et al.

Serial No.:

Group Art Unit: Unassigned

Filing Date: even date

Examiner: Unassigned

Title: NOVEL HCV NON-STRUCTURAL POLYPEPTIDE

STATEMENT TO SUPPORT FILING AND SUBMISSION IN ACCORDANCE
WITH 37 C.F.R. §§ 1.821-1.825

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned hereby states that the content of the attached papers and the computer-readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §§ 1.821(c) and (e), respectively, are the same.

Respectfully submitted,

Date: Nov 22, 2000

By: D. Pasternak
Dahna S. Pasternak
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00231 544260

SEQUENCE LISTING

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Selby, Mark
Houghton, Michael

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gccactggta acaggattag cagagcgagg tatgtaggcg gtgctacaga gttcttgaag			8212
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Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His	20	25	30
Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly	35	40	45
Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly	50	55	60
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser	65	70	75
Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala	85	90	95
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro	100	105	110
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser	115	120	125
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val	130	135	140
Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys	145	150	155
Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala	165	170	175
Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val	180	185	190
Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe	195	200	205
Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe	210	215	220
Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp	225	230	235
Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro	245	250	255
Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe	260	265	270
Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr	275	280	285
Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn	290	295	300
Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly			

305	310	315	320
Val Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr	325	330	335
Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val Ala Tyr Gln Ala Thr	340	345	350
Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp	355	360	365
Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu	370	375	380
Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile Thr Leu Thr His Pro	385	390	395
Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val	405	410	415
Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala	420	425	430
Tyr Cys Leu Ser Thr Gly Cys Val Val Ile Val Gly Arg Val Val Leu	435	440	445
Ser Gly Lys Pro Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Arg Glu	450	455	460
Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln	465	470	475
Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu	485	490	495
Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala Pro Ala Val Gln Thr	500	505	510
Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe	515	520	525
Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn	530	535	540
Pro Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro	545	550	555
Leu Thr Thr Ser Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val	565	570	575
Ala Ala Gln Leu Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala	580	585	590
Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu	595	600	605
Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val			

915										920										925																
Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	Pro	Ser	His	Ile	Thr	Ala	Glu																					
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Ala	Ala	Gly	Arg	Arg	Leu	Ala	Arg	Gly	Ser	Pro	Pro	Ser	Val	Ala	Ser																					
945					950					955					960																					
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					980					985					990																					
Trp	Arg	Gln	Glu	Met	Gly	Gly	Asn	Ile	Thr	Arg	Val	Glu	Ser	Glu	Asn																					
					995					1000					1005																					
Lys	Val	Val	Ile	Leu	Asp	Ser	Phe	Asp	Pro	Leu	Val	Ala	Glu	Glu	Asp																					
1010					1015					1020																										
Glu	Arg	Glu	Ile	Ser	Val	Pro	Ala	Glu	Ile	Leu	Arg	Lys	Ser	Arg	Arg																					
025					1030					1035					1040																					
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Leu	Pro	Ile	Asn	Ala	Leu	Ser	Asn	Ser	Leu	Leu	Arg	His	His	Asn	Leu																					
					1205					1210					1215																					
Val	Tyr	Ser	Thr	Thr	Ser	Arg	Ser	Ala	Cys	Gln	Arg	Gln	Lys	Lys	Val																					

1220	1225	1230
Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu		
1235	1240	1245
Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser		
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Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys		
265	1270	1275 1280
Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val		
1285	1290	1295
Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr		
1300	1305	1310
Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln		
1315	1320	1325
Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp		
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Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr		
345	1350	1355 1360
Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser		
1365	1370	1375
Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys		
1380	1385	1390
Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val		
1395	1400	1405
Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp		
1410	1415	1420
Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu		
425	1430	1435 1440
Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr		
1445	1450	1455
Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr		
1460	1465	1470
Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu		
1475	1480	1485
Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys		
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<220>

<223> Description of Artificial Sequence: pDeltaNS3NS5

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ccatatgaag ctttttgcaa aagcctaggc ctccaaaaaa gcctcctcac tacttctgga 240
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ggggcggaga atgggcggaa ctgggcgggg agggaattat tggctattgg ccattgcata 360
cgttgtatct atatcataat atgtacatct atattggctc atgtccaata tgaccgccat 420
gttgacattg attattgact agttattaat agtaatcaat tacgggggtca ttagttcata 480
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atcaagtgt tcatatgcca agtcggcccc ctattgacgt caatgacggt aaatggcccc 720
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 Met Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu
 1 5 10
 aac ccc tct gtt gct gca aca ctg ggc ttt ggt gct tac atg tcc aag 2079
 Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys
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 gct cat ggg atc gat cct aac atc agg acc ggg gtg aga aca att acc 2127
 Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr
 35 40 45
 act ggc agc ccc atc acg tac tcc acc tac ggc aag ttc ctt gcc gac 2175
 Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp
 50 55 60
 ggc ggg tgc tcg ggg ggc gct tat gac ata ata att tgt gac gag tgc 2223
 Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys
 65 70 75
 cac tcc acg gat gcc aca tcc atc ttg ggc att ggc act gtc ctt gac 2271
 His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp
 80 85 90
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 Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr
 95 100 105 110
 cct ccg ggc tcc gtc act gtg ccc cat ccc aac atc gag gag gtt gct 2367
 Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala
 115 120 125
 ctg tcc acc acc gga gag atc cct ttt tac ggc aag gct atc ccc ctc 2415
 Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu
 130 135 140
 gaa gta atc aag ggg ggg aga cat ctc atc ttc tgt cat tca aag aag 2463
 Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys
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 aag tgc gac gaa ctc gcc gca aag ctg gtc gca ttg ggc atc aat gcc 2511
 Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala
 160 165 170
 gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc atc ccg acc agc ggc 2559

ctg gtc aat cta ctg ccc gcc atc ctc tcg ccc gga gcc ctc gta gtc	3951
Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val	
640 645 650	
ggc gtg gtc tgt gca gca ata ctg cgc cgg cac gtt ggc ccg ggc gag	3999
Gly Val Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu	
655 660 665 670	
ggg gca gtg cag tgg atg aac cgg ctg ata gcc ttc gcc tcc cgg ggg	4047
Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly	
675 680 685	
aac cat gtt tcc ccc acg cac tac gtg ccg gag agc gat gca gct gcc	4095
Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala	
690 695 700	
cgc gtc act gcc ata ctc agc agc ctc act gta acc cag ctc ctg agg	4143
Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg	
705 710 715	
cga ctg cac cag tgg ata agc tcg gag tgt acc act cca tgc tcc ggt	4191
Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly	
720 725 730	
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Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp	
735 740 745 750	
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Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile	
755 760 765	
ccc ttt gtg tcc tgc cag cgc ggg tat aag ggg gtc tgg cga ggg gac	4335
Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp	
770 775 780	
ggc atc atg cac act cgc tgc cac tgt gga gct gag atc act gga cat	4383
Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His	
785 790 795	
gtc aaa aac ggg acg atg agg atc gtc ggt cct agg acc tgc agg aac	4431
Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn	
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atg tgg agt ggg acc ttc ccc att aat gcc tac acc acg ggc ccc tgt	4479
Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys	
815 820 825 830	
acc ccc ctt cct gcg ccg aac tac acg ttc gcg cta tgg agg gtg tct	4527
Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser	
835 840 845	
gca gag gaa tac gtg gag ata agg cag gtg ggg gac ttc cac tac gtg	4575
Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val	
850 855 860	
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gtt cag cct gag aag ggg ggt cgt aag cca gct cgt ctc atc gtg ttc	6015
Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe	
1330 1335 1340	
ccc gat ctg ggc gtg cgc gtg tgc gaa aag atg gct ttg tac gac gtg	6063
Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val	
1345 1350 1355	
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Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln	
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Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser	
1375 1380 1385 1390	
aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc ttt gac tcc	6207
Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser	
1395 1400 1405	
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Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys	
1410 1415 1420	
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Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu	
1425 1430 1435	
agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg gag aac tgc	6351
Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys	
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Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly	
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Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala	
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Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro	
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Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val	
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Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His	
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Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr	
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ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc gtc ctt ata	6831
Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile	
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gcc agg gac cag ctt gaa cag gcc ctc gat tgc gag atc tac ggg gcc	6879
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1615	1620 1625 1630
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Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu	
1635	1640 1645
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His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile	
1650	1655 1660
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Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg	
1665	1670 1675
gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt ctg gcc aga	7071
Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg	
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Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val	
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Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp	
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Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu	
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<211> 1771
<212> PRT
<213> Artificial Sequence

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Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly
35 40 45
Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly
50 55 60
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser
65 70 75 80
Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala
85 90 95
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
100 105 110
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser
115 120 125
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val
130 135 140
Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys
145 150 155 160
Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala
165 170 175

Tyr	Tyr	Arg	Gly	Leu	Asp	Val	Ser	Val	Ile	Pro	Thr	Ser	Gly	Asp	Val	180	185	190	
Val	Val	Val	Ala	Thr	Asp	Ala	Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	195	200	205	
Asp	Ser	Val	Ile	Asp	Cys	Asn	Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	210	215	220	
Ser	Leu	Asp	Pro	Thr	Phe	Thr	Ile	Glu	Thr	Ile	Thr	Leu	Pro	Gln	Asp	225	230	235	240
Ala	Val	Ser	Arg	Thr	Gln	Arg	Arg	Gly	Arg	Thr	Gly	Arg	Gly	Lys	Pro	245	250	255	
Gly	Ile	Tyr	Arg	Phe	Val	Ala	Pro	Gly	Glu	Arg	Pro	Ser	Gly	Met	Phe	260	265	270	
Asp	Ser	Ser	Val	Leu	Cys	Glu	Cys	Tyr	Asp	Ala	Gly	Cys	Ala	Trp	Tyr	275	280	285	
Glu	Leu	Thr	Pro	Ala	Glu	Thr	Thr	Val	Arg	Leu	Arg	Ala	Tyr	Met	Asn	290	295	300	
Thr	Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	His	Leu	Glu	Phe	Trp	Glu	Gly	305	310	315	320
Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	Phe	Leu	Ser	Gln	Thr	325	330	335	
Lys	Gln	Ser	Gly	Glu	Asn	Leu	Pro	Tyr	Leu	Val	Ala	Tyr	Gln	Ala	Thr	340	345	350	
Val	Cys	Ala	Arg	Ala	Gln	Ala	Pro	Pro	Pro	Ser	Trp	Asp	Gln	Met	Trp	355	360	365	
Lys	Cys	Leu	Ile	Arg	Leu	Lys	Pro	Thr	Leu	His	Gly	Pro	Thr	Pro	Leu	370	375	380	
Leu	Tyr	Arg	Leu	Gly	Ala	Val	Gln	Asn	Glu	Ile	Thr	Leu	Thr	His	Pro	385	390	395	400
Val	Thr	Lys	Tyr	Ile	Met	Thr	Cys	Met	Ser	Ala	Asp	Leu	Glu	Val	Val	405	410	415	
Thr	Ser	Thr	Trp	Val	Leu	Val	Gly	Gly	Val	Leu	Ala	Ala	Leu	Ala	Ala	420	425	430	
Tyr	Cys	Leu	Ser	Thr	Gly	Cys	Val	Val	Ile	Val	Gly	Arg	Val	Val	Leu	435	440	445	
Ser	Gly	Lys	Pro	Ala	Ile	Ile	Pro	Asp	Arg	Glu	Val	Leu	Tyr	Arg	Glu	450	455	460	
Phe	Asp	Glu	Met	Glu	Glu	Cys	Ser	Gln	His	Leu	Pro	Tyr	Ile	Glu	Gln	465	470	475	480

Gly	Met	Met	Leu	Ala	Glu	Gln	Phe	Lys	Gln	Lys	Ala	Leu	Gly	Leu	Leu	485	490	495
Gln	Thr	Ala	Ser	Arg	Gln	Ala	Glu	Val	Ile	Ala	Pro	Ala	Val	Gln	Thr	500	505	510
Asn	Trp	Gln	Lys	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	Phe	515	520	525
Ile	Ser	Gly	Ile	Gln	Tyr	Leu	Ala	Gly	Leu	Ser	Thr	Leu	Pro	Gly	Asn	530	535	540
Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ala	Val	Thr	Ser	Pro	545	550	555
Leu	Thr	Thr	Ser	Gln	Thr	Leu	Leu	Phe	Asn	Ile	Leu	Gly	Gly	Trp	Val	565	570	575
Ala	Ala	Gln	Leu	Ala	Ala	Pro	Gly	Ala	Ala	Thr	Ala	Phe	Val	Gly	Ala	580	585	590
Gly	Leu	Ala	Gly	Ala	Ala	Ile	Gly	Ser	Val	Gly	Leu	Gly	Lys	Val	Leu	595	600	605
Ile	Asp	Ile	Leu	Ala	Gly	Tyr	Gly	Ala	Gly	Val	Ala	Gly	Ala	Leu	Val	610	615	620
Ala	Phe	Lys	Ile	Met	Ser	Gly	Glu	Val	Pro	Ser	Thr	Glu	Asp	Leu	Val	625	630	635
Asn	Leu	Leu	Pro	Ala	Ile	Leu	Ser	Pro	Gly	Ala	Leu	Val	Val	Gly	Val	645	650	655
Val	Cys	Ala	Ala	Ile	Leu	Arg	Arg	His	Val	Gly	Pro	Gly	Glu	Gly	Ala	660	665	670
Val	Gln	Trp	Met	Asn	Arg	Leu	Ile	Ala	Phe	Ala	Ser	Arg	Gly	Asn	His	675	680	685
Val	Ser	Pro	Thr	His	Tyr	Val	Pro	Glu	Ser	Asp	Ala	Ala	Ala	Arg	Val	690	695	700
Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	Leu	Leu	Arg	Arg	Leu	705	710	715
His	Gln	Trp	Ile	Ser	Ser	Glu	Cys	Thr	Thr	Pro	Cys	Ser	Gly	Ser	Trp	725	730	735
Leu	Arg	Asp	Ile	Trp	Asp	Trp	Ile	Cys	Glu	Val	Leu	Ser	Asp	Phe	Lys	740	745	750
Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	Pro	Gly	Ile	Pro	Phe	755	760	765
Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	Arg	Gly	Asp	Gly	Ile	770	775	780

Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu
 1090 1095 1100

Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile
 1105 1110 1115 1120

Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys
 1125 1130 1135

Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu
 1140 1145 1150

Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val
 1155 1160 1165

Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys Cys Ser Met Ser Tyr
 1170 1175 1180

Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys
 1185 1190 1195 1200

Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu
 1205 1210 1215

Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val
 1220 1225 1230

Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu
 1235 1240 1245

Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser
 1250 1255 1260

Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys
 1265 1270 1275 1280

Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val
 1285 1290 1295

Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr
 1300 1305 1310

Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln
 1315 1320 1325

Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp
 1330 1335 1340

Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr
 1345 1350 1355 1360

Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser
 1365 1370 1375

Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys
 1380 1385 1390

Thr	Pro	Met	Gly	Phe	Ser	Tyr	Asp	Thr	Arg	Cys	Phe	Asp	Ser	Thr	Val	1395	1400	1405	
Thr	Glu	Ser	Asp	Ile	Arg	Thr	Glu	Glu	Ala	Ile	Tyr	Gln	Cys	Cys	Asp	1410	1415	1420	
Leu	Asp	Pro	Gln	Ala	Arg	Val	Ala	Ile	Lys	Ser	Leu	Thr	Glu	Arg	Leu	425	1430	1435	1440
Tyr	Val	Gly	Gly	Pro	Leu	Thr	Asn	Ser	Arg	Gly	Glu	Asn	Cys	Gly	Tyr	1445	1450	1455	
Arg	Arg	Cys	Arg	Ala	Ser	Gly	Val	Leu	Thr	Thr	Ser	Cys	Gly	Asn	Thr	1460	1465	1470	
Leu	Thr	Cys	Tyr	Ile	Lys	Ala	Arg	Ala	Ala	Cys	Arg	Ala	Ala	Gly	Leu	1475	1480	1485	
Gln	Asp	Cys	Thr	Met	Leu	Val	Cys	Gly	Asp	Asp	Leu	Val	Val	Ile	Cys	1490	1495	1500	
Glu	Ser	Ala	Gly	Val	Gln	Glu	Asp	Ala	Ala	Ser	Leu	Arg	Ala	Phe	Thr	505	1510	1515	1520
Glu	Ala	Met	Thr	Arg	Tyr	Ser	Ala	Pro	Pro	Gly	Asp	Pro	Pro	Gln	Pro	1525	1530	1535	
Glu	Tyr	Asp	Leu	Glu	Leu	Ile	Thr	Ser	Cys	Ser	Ser	Asn	Val	Ser	Val	1540	1545	1550	
Ala	His	Asp	Gly	Ala	Gly	Lys	Arg	Val	Tyr	Tyr	Leu	Thr	Arg	Asp	Pro	1555	1560	1565	
Thr	Thr	Pro	Leu	Ala	Arg	Ala	Ala	Trp	Glu	Thr	Ala	Arg	His	Thr	Pro	1570	1575	1580	
Val	Asn	Ser	Trp	Leu	Gly	Asn	Ile	Ile	Met	Phe	Ala	Pro	Thr	Leu	Trp	585	1590	1595	1600
Ala	Arg	Met	Ile	Leu	Met	Thr	His	Phe	Phe	Ser	Val	Leu	Ile	Ala	Arg	1605	1610	1615	
Asp	Gln	Leu	Glu	Gln	Ala	Leu	Asp	Cys	Glu	Ile	Tyr	Gly	Ala	Cys	Tyr	1620	1625	1630	
Ser	Ile	Glu	Pro	Leu	Asp	Leu	Pro	Pro	Ile	Ile	Gln	Arg	Leu	His	Gly	1635	1640	1645	
Leu	Ser	Ala	Phe	Ser	Leu	His	Ser	Tyr	Ser	Pro	Gly	Glu	Ile	Asn	Arg	1650	1655	1660	
Val	Ala	Ala	Cys	Leu	Arg	Lys	Leu	Gly	Val	Pro	Pro	Leu	Arg	Ala	Trp	665	1670	1675	1680
Arg	His	Arg	Ala	Arg	Ser	Val	Arg	Ala	Arg	Leu	Leu	Ala	Arg	Gly	Gly	1685	1690	1695	

Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr
 1700 1705 1710

Lys Leu Lys Leu Thr Pro Ile Ala Ala Gly Gln Leu Asp Leu Ser
 1715 1720 1725

Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val
 1730 1735 1740

Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala
 745 1750 1755 1760

Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg
 1765 1770

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<211> 4282

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: pCMVII

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0022164260

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<211> 6299

<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: pNS34a

<220>
<221> CDS
<222> (1990)..(4047)

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gga gcc ctc gta gtc ggc gtg gtc tgt gca gca ata ctg cgc cgg cac Gly Ala Leu Val Val Gly Val Val Cys Ala Ala Ile Leu Arg Arg His 650 655 660 665			14739
gtt ggc ccg ggc gag ggg gca gtg cag tgg atg aac cgg ctg ata gcc Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala 670 675 680			14787
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Gln	Leu	Pro	Gly	Ile	Pro	Phe	Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	
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Val	Trp	Arg	Gly	Asp	Gly	Ile	Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	
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Glu	Ile	Thr	Gly	His	Val	Lys	Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	
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agg	acc	tgc	agg	aac	atg	tgg	agt	ggg	acc	ttc	ccc	att	aat	gcc	tac	15219
Arg	Thr	Cys	Arg	Asn	Met	Trp	Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	
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acc	acg	ggc	ccc	tgt	acc	ccc	ctt	cct	gcg	ccg	aac	tac	acg	ttc	gcg	15267
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Leu	Trp	Arg	Val	Ser	Ala	Glu	Glu	Tyr	Val	Glu	Ile	Arg	Gln	Val	Gly	
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Asp	Phe	His	Tyr	Val	Thr	Gly	Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	
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Cys	Gln	Val	Pro	Ser	Pro	Glu	Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	
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Cys	Glu	Pro	Glu	Pro	Asp	Val	Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	
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Thr Thr Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala	
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gcc tgt cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc	17235
Ala Cys Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly	
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Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala	
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Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro	
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Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser	
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Cys Ser Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val	
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Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp	
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Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile	
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atg ttt gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc	17571
Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe	
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Phe Ser Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys	
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Glu Ile Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro	
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Ile Ile Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr	
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Ser Pro Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly	
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<213> Artificial Sequence

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Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly
35 40 45

Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly
50 55 60

Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser
65 70 75 80

Val	Ser	Pro	Thr	His	Tyr	Val	Pro	Glu	Ser	Asp	Ala	Ala	Ala	Arg	Val	690	695	700	
Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	Leu	Leu	Arg	Arg	Leu	705	710	715	720
His	Gln	Trp	Ile	Ser	Ser	Glu	Cys	Thr	Thr	Pro	Cys	Ser	Gly	Ser	Trp	725	730	735	
Leu	Arg	Asp	Ile	Trp	Asp	Trp	Ile	Cys	Glu	Val	Leu	Ser	Asp	Phe	Lys	740	745	750	
Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	Pro	Gly	Ile	Pro	Phe	755	760	765	
Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	Arg	Gly	Asp	Gly	Ile	770	775	780	
Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	Glu	Ile	Thr	Gly	His	Val	Lys	785	790	795	800
Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	Arg	Thr	Cys	Arg	Asn	Met	Trp	805	810	815	
Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	Gly	Pro	Cys	Thr	Pro	820	825	830	
Leu	Pro	Ala	Pro	Asn	Tyr	Thr	Phe	Ala	Leu	Trp	Arg	Val	Ser	Ala	Glu	835	840	845	
Glu	Tyr	Val	Glu	Ile	Arg	Gln	Val	Gly	Asp	Phe	His	Tyr	Val	Thr	Gly	850	855	860	
Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	Cys	Gln	Val	Pro	Ser	Pro	Glu	865	870	875	880
Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	Arg	Phe	Ala	Pro	Pro	885	890	895	
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Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	Pro	Ser	His	Ile	Thr	Ala	Glu	930	935	940	
Ala	Ala	Gly	Arg	Arg	Leu	Ala	Arg	Gly	Ser	Pro	Pro	Ser	Val	Ala	Ser	945	950	955	960
Ser	Ser	Ala	Ser	Gln	Leu	Ser	Ala	Pro	Ser	Leu	Lys	Ala	Thr	Cys	Thr	965	970	975	
Ala	Asn	His	Asp	Ser	Pro	Asp	Ala	Glu	Leu	Ile	Glu	Ala	Asn	Leu	Leu	980	985	990	

Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr
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Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln
 1315 1320 1325

Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp
 1330 1335 1340

Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr
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Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys
 1380 1385 1390

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 1555 1560 1565

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Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg
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Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr
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Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly
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Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg
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Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp
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Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly
1685 1690 1695

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1730 1735 1740

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<223> Description of Artificial Sequence:
pd.deltaNS3NS5.pj

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Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr	
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Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile	
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Thr Leu Pro Gln Asp Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr	
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Gly Arg Gly Lys Pro Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg	
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Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala	
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Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu	
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Arg Ala Tyr Met Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu	
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Glu Phe Trp Glu Gly Val Phe Thr Gly Leu Thr His Ile Asp Ala His	
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Phe Leu Ser Gln Thr Lys Gln Ser Gly Glu Asn Leu Pro Tyr Leu Val	
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Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser	
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Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His	
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Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Ile	
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Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala	
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Asp Leu Glu Val Val Thr Ser Thr Trp Val Leu Val Gly Gly Val Leu	
415 420 425	
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Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala			
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Ser Arg Gly Asn His Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp			
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Ala Ala Ala Arg Val Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln			
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ctc ctg agg cga ctg cac cag tgg ata agc tcg gag tgt acc act cca			14871
Leu Leu Arg Arg Leu His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro			
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Cys Ser Gly Ser Trp Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val			
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Leu Ser Asp Phe Lys Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu			
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Pro Gly Ile Pro Phe Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp			
765	770	775	
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Arg Gly Asp Gly Ile Met His Thr Arg Cys His Cys Gly Ala Glu Ile			
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Thr Gly His Val Lys Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr			
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Cys Arg Asn Met Trp Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr			
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Gly Pro Cys Thr Pro Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp			
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Arg Val Ser Ala Glu Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe			
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cac tac gtg acg ggt atg act act gac aat ctt aaa tgc ccg tgc cag			15303
His Tyr Val Thr Gly Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln			
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Val Pro Ser Pro Glu Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His			
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Arg Phe Ala Pro Pro Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe	
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Arg Val Gly Leu His Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu	
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Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser	
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His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro	
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Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu	
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Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile	
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Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu	
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Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro	
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Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro	
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Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr	
1085 1090 1095	
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Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser	
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Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys				
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Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile				
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Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly				
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Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys				
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Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser				
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Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly				
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Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser				
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tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac				17367
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Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr				
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Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe	
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Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn	
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 <212> PRT
 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:

pd.deltaNS3NS5.pj

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35 40 45
Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly
50 55 60
Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser
65 70 75 80
Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala
85 90 95
Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
100 105 110
Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser
115 120 125
Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val
130 135 140
Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys
145 150 155 160
Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala
165 170 175
Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val
180 185 190
Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe
195 200 205
Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe
210 215 220
Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile Thr Leu Pro Gln Asp
225 230 235 240
Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro
245 250 255
Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe
260 265 270
Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr

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Thr	Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	His	Leu	Glu	Phe	Trp	Glu	Gly
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Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	Phe	Leu	Ser	Gln	Thr
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Lys	Gln	Ser	Gly	Glu	Asn	Leu	Pro	Tyr	Leu	Val	Ala	Tyr	Gln	Ala	Thr
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Val	Cys	Ala	Arg	Ala	Gln	Ala	Pro	Pro	Pro	Ser	Trp	Asp	Gln	Met	Trp
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Lys	Cys	Leu	Ile	Arg	Leu	Lys	Pro	Thr	Leu	His	Gly	Pro	Thr	Pro	Leu
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Tyr	Cys	Leu	Ser	Thr	Gly	Cys	Val	Val	Ile	Val	Gly	Arg	Val	Val	Leu
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Asn	Trp	Gln	Lys	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	Phe
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Ile	Ser	Gly	Ile	Gln	Tyr	Leu	Ala	Gly	Leu	Ser	Thr	Leu	Pro	Gly	Asn
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Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ala	Val	Thr	Ser	Pro
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Ala	Ala	Gln	Leu	Ala	Ala	Pro	Gly	Ala	Ala	Thr	Ala	Phe	Val	Gly	Ala

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Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val		
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Ala Phe Lys Ile Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val		
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Val Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala		
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Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His		
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Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val		
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His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp		
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Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys		
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Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe		
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Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile		
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Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys		
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Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val Thr Gly		
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Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu		
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Glu Tyr Pro	Val Gly Ser	Gln Leu Pro	Cys Glu Pro	Glu Pro Asp Val	
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Thr Gly Asp	Asn Thr Thr	Thr Ser Ser	Glu Pro Ala	Pro Ser Gly Cys	
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Pro Pro Asp	Ser Asp Ala	Glu Ser Tyr	Ser Ser Met	Pro Pro Leu Glu	
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Gly Glu Pro	Gly Asp Pro	Asp Leu Ser	Asp Gly Ser	Trp Ser Thr Val	
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Ser Ser Glu	Ala Asn Ala	Glu Asp Val	Val Cys Cys	Ser Met Ser Tyr	
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Ser Trp Thr	Gly Ala Leu	Val Thr Pro	Cys Ala Ala	Glu Glu Gln Lys	

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Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys	1265	1270	1275
Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val	1285	1290	1295
Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu Glu Asp Asn Val Thr	1300	1305	1310
Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln	1315	1320	1325
Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp	1330	1335	1340
Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr	1345	1350	1355
Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser	1365	1370	1375
Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys	1380	1385	1390
Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val	1395	1400	1405
Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp	1410	1415	1420
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Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr	1460	1465	1470
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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:
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<220>

<221> CDS

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<400> 12

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His	Tyr	Val	Thr	Gly	Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	Cys	Gln	
	860				865					870					875	
gtc	cca	tcg	ccc	gaa	ttt	ttc	aca	gaa	ttg	gac	ggg	gtg	cgc	cta	cat	15351
Val	Pro	Ser	Pro	Glu	Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	
				880					885					890		
agg	ttt	gcg	ccc	ccc	tgc	aag	ccc	ttg	ctg	cgg	gag	gag	gta	tca	ttc	15399
Arg	Phe	Ala	Pro	Pro	Cys	Lys	Pro	Leu	Leu	Arg	Glu	Glu	Val	Ser	Phe	
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Arg	Val	Gly	Leu	His	Glu	Tyr	Pro	Val	Gly	Ser	Gln	Leu	Pro	Cys	Glu	
	910						915					920				
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Pro	Glu	Pro	Asp	Val	Ala	Val	Leu	Thr	Ser	Met	Leu	Thr	Asp	Pro	Ser	
	925					930					935					
cat	ata	aca	gca	gag	gcg	gcc	ggg	cga	agg	ttg	gcg	agg	gga	tca	ccc	15543
His	Ile	Thr	Ala	Glu	Ala	Ala	Gly	Arg	Arg	Leu	Ala	Arg	Gly	Ser	Pro	
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ccc	tct	gtg	gcc	agc	tcc	tcg	gct	agc	cag	cta	tcc	gct	cca	tct	ctc	15591
Pro	Ser	Val	Ala	Ser	Ser	Ser	Ala	Ser	Gln	Leu	Ser	Ala	Pro	Ser	Leu	
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Lys	Ala	Thr	Cys	Thr	Ala	Asn	His	Asp	Ser	Pro	Asp	Ala	Glu	Leu	Ile	
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gag	gcc	aac	ctc	cta	tgg	agg	cag	gag	atg	ggc	ggc	aac	atc	acc	agg	15687
Glu	Ala	Asn	Leu	Leu	Trp	Arg	Gln	Glu	Met	Gly	Gly	Asn	Ile	Thr	Arg	
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Val	Glu	Ser	Glu	Asn	Lys	Val	Val	Ile	Leu	Asp	Ser	Phe	Asp	Pro	Leu	
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Val	Ala	Glu	Glu	Asp	Glu	Arg	Glu	Ile	Ser	Val	Pro	Ala	Glu	Ile	Leu	

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Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro				
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Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu				
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cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct				15927
Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro				
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Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr				
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cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc				16023
Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser				
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tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct gag ccc				16071
Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro				
1120	1125	1130		
gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc				16119
Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser				
1135	1140	1145		
atg ccc ccc ctg gag ggg gag cct ggg gat ccg gat ctt agc gac ggg				16167
Met Pro Pro Leu Glu Gly Glu Pro Gly Asp Pro Asp Leu Ser Asp Gly				
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Ser Trp Ser Thr Val Ser Ser Glu Ala Asn Ala Glu Asp Val Val Cys				
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Cys Ser Met Ser Tyr Ser Trp Thr Gly Ala Leu Val Thr Pro Cys Ala				
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Ala Glu Glu Gln Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu				
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cgt cac cac aat ttg gtg tat tcc acc acc tca cgc agt gct tgc caa				16359
Arg His His Asn Leu Val Tyr Ser Thr Thr Ser Arg Ser Ala Cys Gln				
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Arg Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Ser His				
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Tyr Gln Asp Val Leu Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys				
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Ala Asn Leu Leu Ser Val Glu Glu Ala Cys Ser Leu Thr Pro Pro His	
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Ser Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Cys His	
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gcc aga aag gcc gta acc cac atc aac tcc gtg tgg aaa gac ctt ctg	16599
Ala Arg Lys Ala Val Thr His Ile Asn Ser Val Trp Lys Asp Leu Leu	
1295 1300 1305	
gaa gac aat gta aca cca ata gac act acc atc atg gct aag aac gag	16647
Glu Asp Asn Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu	
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Val Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu	
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Ile Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu	
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Tyr Asp Val Val Thr Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr	
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Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala	
1375 1380 1385	
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Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys	
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Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile	
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Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser	
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ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg	17031
Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly	
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Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr	
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agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt	17127
Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys	
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Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp
 1485 1490 1495

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 Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser
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 Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly
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 Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser
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 Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr
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 Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser
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 Val Leu Ile Ala Arg Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile
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 Tyr Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile
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 Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro
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 Gly Glu Ile Asn Arg Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro
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ccc ttg cga gct tgg aga cac cgg gcc cgg agc gtc cgc gct agg ctt 17751
 Pro Leu Arg Ala Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu
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 Leu Ala Arg Gly Gly Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn
 1695 1700 1705

tgg gca gta aga aca aag ctc aaa ctc act cca ata gcg gcc gct ggc 17847
 Trp Ala Val Arg Thr Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly

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Gln Leu Asp Leu Ser Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp			
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att tat cac agc gtg tct cat gcc cgg ccc cgc tgg atc tgg ttt tgc			17943
Ile Tyr His Ser Val Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys			
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cta ctc ctg ctt gct gca ggg gta ggc atc tac ctc ctc ccc aac cga			17991
Leu Leu Leu Leu Ala Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg			
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Met Ser Thr Asn Pro Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn			
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Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly			
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Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala			
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Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro			
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atc ccc aag gct cgt cgg ccc gag ggc agg acc tgg gct cag ccc ggg			18231
Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly			
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tac cct tgg ccc ctc tat ggc aat gag ggc tgc ggg tgg gcg gga tgg			18279
Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp			
1855	1860	1865	
ctc ctg tct ccc cgt ggc tct cgg cct agc tgg ggc ccc aca gac ccc			18327
Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro			
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cgg cgt agg tcg cgc aat ttg ggt aag taatagtcga ctttgttccc			18374
Arg Arg Arg Ser Arg Asn Leu Gly Lys			
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35 40 45

Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly
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Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser
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Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala
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Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
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Gly Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser
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Ile Lys Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys
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Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val
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Val Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe
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Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe
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Ala Val Ser Arg Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro
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Gly Ile Tyr Arg Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe
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Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn
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Asn	Leu	Leu	Pro	Ala	Ile	Leu	Ser	Pro	Gly	Ala	Leu	Val	Val	Gly	Val	645	650	655
Val	Cys	Ala	Ala	Ile	Leu	Arg	Arg	His	Val	Gly	Pro	Gly	Glu	Gly	Ala	660	665	670
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Val	Ser	Pro	Thr	His	Tyr	Val	Pro	Glu	Ser	Asp	Ala	Ala	Ala	Arg	Val	690	695	700
Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	Leu	Leu	Arg	Arg	Leu	705	710	715
His	Gln	Trp	Ile	Ser	Ser	Glu	Cys	Thr	Thr	Pro	Cys	Ser	Gly	Ser	Trp	725	730	735
Leu	Arg	Asp	Ile	Trp	Asp	Trp	Ile	Cys	Glu	Val	Leu	Ser	Asp	Phe	Lys	740	745	750
Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	Pro	Gly	Ile	Pro	Phe	755	760	765
Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	Arg	Gly	Asp	Gly	Ile	770	775	780
Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	Glu	Ile	Thr	Gly	His	Val	Lys	785	790	795
Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	Arg	Thr	Cys	Arg	Asn	Met	Trp	805	810	815
Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	Gly	Pro	Cys	Thr	Pro	820	825	830
Leu	Pro	Ala	Pro	Asn	Tyr	Thr	Phe	Ala	Leu	Trp	Arg	Val	Ser	Ala	Glu	835	840	845
Glu	Tyr	Val	Glu	Ile	Arg	Gln	Val	Gly	Asp	Phe	His	Tyr	Val	Thr	Gly	850	855	860
Met	Thr	Thr	Asp	Asn	Leu	Lys	Cys	Pro	Cys	Gln	Val	Pro	Ser	Pro	Glu	865	870	875
Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	Arg	Phe	Ala	Pro	Pro	885	890	895
Cys	Lys	Pro	Leu	Leu	Arg	Glu	Glu	Val	Ser	Phe	Arg	Val	Gly	Leu	His	900	905	910

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 Lys Glu Val Lys Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser
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 Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg
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 Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr
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 Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu
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Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg
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Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg
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Glu	Phe	Trp	Glu	Gly	Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	
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Phe	Leu	Ser	Gln	Thr	Lys	Gln	Ser	Gly	Glu	Asn	Leu	Pro	Tyr	Leu	Val	

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Gln Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro
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pd.delta.NS3NS5.pj.core140

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Ser	Pro	Ile	Thr	Tyr	Ser	Thr	Tyr	Gly	Lys	Phe	Leu	Ala	Asp	Gly	Gly	
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Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr
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 Glu Leu Thr Pro Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn
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 Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly
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 Phe Asp Glu Met Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln
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 Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu
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Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu
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Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val
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Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His
675 680 685

Val Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val
690 695 700

Thr Ala Ile Leu Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu
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His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp
725 730 735

Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys
740 745 750

Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe
755 760 765

Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile
770 775 780

Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys
785 790 795 800

Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp
805 810 815

Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro
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Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser Ala Glu
835 840 845

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850 855 860

Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu
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	Met	Ala	Ala	Tyr	Ala	Ala	Gln	Gly	Tyr	Lys	Val	
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Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr												
	15				20				25			
atg tcc aag gct cat ggg atc gat cct aac atc agg acc ggg gtg aga												12807
Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg												
	30				35				40			
aca att acc act ggc agc ccc atc acg tac tcc acc tac ggc aag ttc												12855
Thr Ile Thr Thr Gly Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe												
	45				50				55			
ctt gcc gac ggc ggg tgc tcg ggg ggc gct tat gac ata ata att tgt												12903
Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys												
	60				65				70			75
gac gag tgc cac tcc acg gat gcc aca tcc atc ttg ggc att ggc act												12951
Asp Glu Cys His Ser Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr												
				80					85			90
gtc ctt gac caa gca gag act gcg ggg gcg aga ctg gtt gtg ctc gcc												12999
Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala												
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acc gcc acc cct ccg ggc tcc gtc act gtg ccc cat ccc aac atc gag												13047
Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu												
				110					115			120
gag gtt gct ctg tcc acc acc gga gag atc cct ttt tac ggc aag gct												13095
Glu Val Ala Leu Ser Thr Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala												
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atc ccc ctc gaa gta atc aag ggg ggg aga cat ctc atc ttc tgt cat												13143
Ile Pro Leu Glu Val Ile Lys Gly Gly Arg His Leu Ile Phe Cys His												
	140				145				150			155
tca aag aag aag tgc gac gaa ctc gcc gca aag ctg gtc gca ttg ggc												13191
Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Val Ala Leu Gly												
				160					165			170
atc aat gcc gtg gcc tac tac cgc ggt ctt gac gtg tcc gtc atc ccg												13239
Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro												
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acc agc ggc gat gtt gtc gtc gtg gca acc gat gcc ctc atg acc ggc												13287
Thr Ser Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly												
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tat acc ggc gac ttc gac tcg gtg ata gac tgc aat acg tgt gtc acc												13335
Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr												
				205					210			215
cag aca gtc gat ttc agc ctt gac cct acc ttc acc att gag aca atc												13383
Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Ile												

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	335 340 345			
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	350 355 360			
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	365 370 375			
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	380 385 390 395			
acc ctg acg cac cca gtc acc aaa tac atc atg aca tgc atg tcg gcc	Thr Leu Thr His Pro Val Thr Lys Tyr Ile Met Thr Cys Met Ser Ala	13911		
	400 405 410			
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	415 420 425			
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	430 435 440			
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	445 450 455			

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Pro Tyr Ile Glu Gln Gly Met Met Leu Ala Glu Gln Phe Lys Gln Lys	
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Ala Leu Gly Leu Leu Gln Thr Ala Ser Arg Gln Ala Glu Val Ile Ala	
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Pro Ala Val Gln Thr Asn Trp Gln Lys Leu Glu Thr Phe Trp Ala Lys	
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His Met Trp Asn Phe Ile Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser	
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Ala Phe Val Gly Ala Gly Leu Ala Gly Ala Ala Ile Gly Ser Val Gly	
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Leu Gly Lys Val Leu Ile Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val	
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Thr Glu Asp Leu Val Asn Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala	
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Pro Gly Glu Gly Ala Val Gln Trp Met Asn Arg Leu Ile Ala Phe Ala	
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Ala	Ala	Ala	Arg	Val	Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	
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tgc	tcc	ggc	tcc	tgg	cta	agg	gac	atc	tgg	gac	tgg	ata	tgc	gag	gtg	14919
Cys	Ser	Gly	Ser	Trp	Leu	Arg	Asp	Ile	Trp	Asp	Trp	Ile	Cys	Glu	Val	
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Leu	Ser	Asp	Phe	Lys	Thr	Trp	Leu	Lys	Ala	Lys	Leu	Met	Pro	Gln	Leu	
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Pro	Gly	Ile	Pro	Phe	Val	Ser	Cys	Gln	Arg	Gly	Tyr	Lys	Gly	Val	Trp	
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Arg	Gly	Asp	Gly	Ile	Met	His	Thr	Arg	Cys	His	Cys	Gly	Ala	Glu	Ile	
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Thr	Gly	His	Val	Lys	Asn	Gly	Thr	Met	Arg	Ile	Val	Gly	Pro	Arg	Thr	
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Cys	Arg	Asn	Met	Trp	Ser	Gly	Thr	Phe	Pro	Ile	Asn	Ala	Tyr	Thr	Thr	
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Val	Pro	Ser	Pro	Glu	Phe	Phe	Thr	Glu	Leu	Asp	Gly	Val	Arg	Leu	His	
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Arg	Phe	Ala	Pro	Pro	Cys	Lys	Pro	Leu	Leu	Arg	Glu	Glu	Val	Ser	Phe	
			895					900					905			
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Arg	Val	Gly	Leu	His	Glu	Tyr	Pro	Val	Gly	Ser	Gln	Leu	Pro	Cys	Glu	

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Pro Glu Pro Asp Val Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser			
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His Ile Thr Ala Glu Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro			
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ccc tct gtg gcc agc tcc tcg gct agc cag cta tcc gct cca tct ctc			15591
Pro Ser Val Ala Ser Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu			
	960	965	970
aag gca act tgc acc gct aac cat gac tcc cct gat gct gag ctc ata			15639
Lys Ala Thr Cys Thr Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile			
	975	980	985
gag gcc aac ctc cta tgg agg cag gag atg ggc ggc aac atc acc agg			15687
Glu Ala Asn Leu Leu Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg			
	990	995	1000
gtt gag tca gaa aac aaa gtg gtg att ctg gac tcc ttc gat ccg ctt			15735
Val Glu Ser Glu Asn Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu			
1005	1010	1015	
gtg gcg gag gag gac gag cgg gag atc tcc gta ccc gca gaa atc ctg			15783
Val Ala Glu Glu Asp Glu Arg Glu Ile Ser Val Pro Ala Glu Ile Leu			
1020	1025	1030	1035
cgg aag tct cgg aga ttc gcc cag gcc ctg ccc gtt tgg gcg cgg ccg			15831
Arg Lys Ser Arg Arg Phe Ala Gln Ala Leu Pro Val Trp Ala Arg Pro			
	1040	1045	1050
gac tat aac ccc ccg cta gtg gag acg tgg aaa aag ccc gac tac gaa			15879
Asp Tyr Asn Pro Pro Leu Val Glu Thr Trp Lys Lys Pro Asp Tyr Glu			
	1055	1060	1065
cca cct gtg gtc cat ggc tgc ccg ctt cca cct cca aag tcc cct cct			15927
Pro Pro Val Val His Gly Cys Pro Leu Pro Pro Pro Lys Ser Pro Pro			
1070	1075	1080	
gtg cct ccg cct cgg aag aag cgg acg gtg gtc ctc act gaa tca acc			15975
Val Pro Pro Pro Arg Lys Lys Arg Thr Val Val Leu Thr Glu Ser Thr			
1085	1090	1095	
cta tct act gcc ttg gcc gag ctc gcc acc aga agc ttt ggc agc tcc			16023
Leu Ser Thr Ala Leu Ala Glu Leu Ala Thr Arg Ser Phe Gly Ser Ser			
1100	1105	1110	1115
tca act tcc ggc att acg ggc gac aat acg aca aca tcc tct gag ccc			16071
Ser Thr Ser Gly Ile Thr Gly Asp Asn Thr Thr Thr Ser Ser Glu Pro			
	1120	1125	1130
gcc cct tct ggc tgc ccc ccc gac tcc gac gct gag tcc tat tcc tcc			16119
Ala Pro Ser Gly Cys Pro Pro Asp Ser Asp Ala Glu Ser Tyr Ser Ser			
	1135	1140	1145

Gly Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala	
1375 1380 1385	
tgg aag tcc aag aaa acc cca atg ggg ttc tcg tat gat acc cgc tgc	16887
Trp Lys Ser Lys Lys Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys	
1390 1395 1400	
ttt gac tcc aca gtc act gag agc gac atc cgt acg gag gag gca atc	16935
Phe Asp Ser Thr Val Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile	
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tac caa tgt tgt gac ctc gac ccc caa gcc cgc gtg gcc atc aag tcc	16983
Tyr Gln Cys Cys Asp Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser	
1420 1425 1430 1435	
ctc acc gag agg ctt tat gtt ggg ggc cct ctt acc aat tca agg ggg	17031
Leu Thr Glu Arg Leu Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly	
1440 1445 1450	
gag aac tgc ggc tat cgc agg tgc cgc gcg agc ggc gta ctg aca act	17079
Glu Asn Cys Gly Tyr Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr	
1455 1460 1465	
agc tgt ggt aac acc ctc act tgc tac atc aag gcc cgg gca gcc tgt	17127
Ser Cys Gly Asn Thr Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys	
1470 1475 1480	
cga gcc gca ggg ctc cag gac tgc acc atg ctc gtg tgt ggc gac gac	17175
Arg Ala Ala Gly Leu Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp	
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Leu Val Val Ile Cys Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser	
1500 1505 1510 1515	
ctg aga gcc ttc acg gag gct atg acc agg tac tcc gcc ccc cct ggg	17271
Leu Arg Ala Phe Thr Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly	
1520 1525 1530	
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Asp Pro Pro Gln Pro Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser	
1535 1540 1545	
tcc aac gtg tca gtc gcc cac gac ggc gct gga aag agg gtc tac tac	17367
Ser Asn Val Ser Val Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr	
1550 1555 1560	
ctc acc cgt gac cct aca acc ccc ctc gcg aga gct gcg tgg gag aca	17415
Leu Thr Arg Asp Pro Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr	
1565 1570 1575	
gca aga cac act cca gtc aat tcc tgg cta ggc aac ata atc atg ttt	17463
Ala Arg His Thr Pro Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe	
1580 1585 1590 1595	
gcc ccc aca ctg tgg gcg agg atg ata ctg atg acc cat ttc ttt agc	17511
Ala Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser	

atc ccc aag gct cgt cgg ccc gag ggc agg acc tgg gct cag ccc ggg 18231
 Ile Pro Lys Ala Arg Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly
 1840 1845 1850

 tac cct tgg ccc ctc tat ggc aat gag ggc tgc ggg tgg gcg gga tgg 18279
 Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp
 1855 1860 1865

 ctc ctg tct ccc cgt ggc tct cgg cct agc tgg ggc ccc aca gac ccc 18327
 Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro
 1870 1875 1880

 cgg cgt agg tcg cgc aat ttg ggt aag gtc atc gat acc ctt acg tgc 18375
 Arg Arg Arg Ser Arg Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys
 1885 1890 1895

 ggc ttc gcc gac ctc atg ggg tac ata ccg ctc gtc ggc gcc cct ctt 18423
 Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu
 1900 1905 1910 1915

 gga ggc gct gcc agg gcc taatagtcga ctttgttccc actgtacttt 18471
 Gly Gly Ala Ala Arg Ala
 1920

 tagctcgtac aaaatacaat atacttttca tttctccgta aacaacatgt tttcccatgt 18531
 aatatccttt tctatttttc gttccgttac caactttaca catactttat atagctattc 18591
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 <212> PRT
 <213> Artificial Sequence

<220>
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 20 25 30
 Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly
 35 40 45
 Ser Pro Ile Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly
 50 55 60
 Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser
 65 70 75 80
 Thr Asp Ala Thr Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala
 85 90 95
 Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro
 100 105 110

Thr	Ser	Thr	Trp	Val	Leu	Val	Gly	Gly	Val	Leu	Ala	Ala	Leu	Ala	Ala		
				420				425					430				
Tyr	Cys	Leu	Ser	Thr	Gly	Cys	Val	Val	Ile	Val	Gly	Arg	Val	Val	Leu		
		435					440					445					
Ser	Gly	Lys	Pro	Ala	Ile	Ile	Pro	Asp	Arg	Glu	Val	Leu	Tyr	Arg	Glu		
		450				455					460						
Phe	Asp	Glu	Met	Glu	Glu	Cys	Ser	Gln	His	Leu	Pro	Tyr	Ile	Glu	Gln		
465					470					475					480		
Gly	Met	Met	Leu	Ala	Glu	Gln	Phe	Lys	Gln	Lys	Ala	Leu	Gly	Leu	Leu		
				485					490					495			
Gln	Thr	Ala	Ser	Arg	Gln	Ala	Glu	Val	Ile	Ala	Pro	Ala	Val	Gln	Thr		
			500					505					510				
Asn	Trp	Gln	Lys	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	Phe		
		515					520					525					
Ile	Ser	Gly	Ile	Gln	Tyr	Leu	Ala	Gly	Leu	Ser	Thr	Leu	Pro	Gly	Asn		
		530				535					540						
Pro	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ala	Val	Thr	Ser	Pro		
545					550				555						560		
Leu	Thr	Thr	Ser	Gln	Thr	Leu	Leu	Phe	Asn	Ile	Leu	Gly	Gly	Trp	Val		
				565					570					575			
Ala	Ala	Gln	Leu	Ala	Ala	Pro	Gly	Ala	Ala	Thr	Ala	Phe	Val	Gly	Ala		
			580					585					590				
Gly	Leu	Ala	Gly	Ala	Ala	Ile	Gly	Ser	Val	Gly	Leu	Gly	Lys	Val	Leu		
		595					600					605					
Ile	Asp	Ile	Leu	Ala	Gly	Tyr	Gly	Ala	Gly	Val	Ala	Gly	Ala	Leu	Val		
	610					615					620						
Ala	Phe	Lys	Ile	Met	Ser	Gly	Glu	Val	Pro	Ser	Thr	Glu	Asp	Leu	Val		
625				630						635				640			
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Val	Cys	Ala	Ala	Ile	Leu	Arg	Arg	His	Val	Gly	Pro	Gly	Glu	Gly	Ala		
			660					665					670				
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		675				680						685					
Val	Ser	Pro	Thr	His	Tyr	Val	Pro	Glu	Ser	Asp	Ala	Ala	Ala	Arg	Val		
		690				695					700						
Thr	Ala	Ile	Leu	Ser	Ser	Leu	Thr	Val	Thr	Gln	Leu	Leu	Arg	Arg	Leu		
705					710					715					720		

His Gln Trp Ile Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp
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 Leu Arg Asp Ile Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys
 740 745 750
 Thr Trp Leu Lys Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe
 755 760 765
 Val Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile
 770 775 780
 Met His Thr Arg Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys
 785 790 795 800
 Asn Gly Thr Met Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp
 805 810 815
 Ser Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro
 820 825 830
 Leu Pro Ala Pro Asn Tyr Thr Phe Ala Leu Trp Arg Val Ser Ala Glu
 835 840 845
 Glu Tyr Val Glu Ile Arg Gln Val Gly Asp Phe His Tyr Val Thr Gly
 850 855 860
 Met Thr Thr Asp Asn Leu Lys Cys Pro Cys Gln Val Pro Ser Pro Glu
 865 870 875 880
 Phe Phe Thr Glu Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro
 885 890 895
 Cys Lys Pro Leu Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His
 900 905 910
 Glu Tyr Pro Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val
 915 920 925
 Ala Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu
 930 935 940
 Ala Ala Gly Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Val Ala Ser
 945 950 955 960
 Ser Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr
 965 970 975
 Ala Asn His Asp Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu
 980 985 990
 Trp Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn
 995 1000 1005
 Lys Val Val Ile Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp
 1010 1015 1020

Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp
1330 1335 1340

Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Thr
345 1350 1355 1360

Lys Leu Pro Leu Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser
1365 1370 1375

Pro Gly Gln Arg Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys
1380 1385 1390

Thr Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val
1395 1400 1405

Thr Glu Ser Asp Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp
1410 1415 1420

Leu Asp Pro Gln Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu
425 1430 1435 1440

Tyr Val Gly Gly Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr
1445 1450 1455

Arg Arg Cys Arg Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr
1460 1465 1470

Leu Thr Cys Tyr Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu
1475 1480 1485

Gln Asp Cys Thr Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys
1490 1495 1500

Glu Ser Ala Gly Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr
505 1510 1515 1520

Glu Ala Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro
1525 1530 1535

Glu Tyr Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val
1540 1545 1550

Ala His Asp Gly Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro
1555 1560 1565

Thr Thr Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro
1570 1575 1580

Val Asn Ser Trp Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp
585 1590 1595 1600

Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg
1605 1610 1615

Asp Gln Leu Glu Gln Ala Leu Asp Cys Glu Ile Tyr Gly Ala Cys Tyr
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Ser Ile Glu Pro Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly
 1635 1640 1645
 Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg
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 Val Ala Ala Cys Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp
 665 1670 1675 1680
 Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu Ala Arg Gly Gly
 1685 1690 1695
 Arg Ala Ala Ile Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr
 1700 1705 1710
 Lys Leu Lys Leu Thr Pro Ile Ala Ala Ala Gly Gln Leu Asp Leu Ser
 1715 1720 1725
 Gly Trp Phe Thr Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val
 1730 1735 1740
 Ser His Ala Arg Pro Arg Trp Ile Trp Phe Cys Leu Leu Leu Leu Ala
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 Ala Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg Met Ser Thr Asn Pro
 1765 1770 1775
 Lys Pro Gln Arg Lys Thr Lys Arg Asn Thr Asn Arg Arg Pro Gln Asp
 1780 1785 1790
 Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly Gly Val Tyr Leu Leu
 1795 1800 1805
 Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala Thr Arg Lys Thr Ser
 1810 1815 1820
 Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro Ile Pro Lys Ala Arg
 825 1830 1835 1840
 Arg Pro Glu Gly Arg Thr Trp Ala Gln Pro Gly Tyr Pro Trp Pro Leu
 1845 1850 1855
 Tyr Gly Asn Glu Gly Cys Gly Trp Ala Gly Trp Leu Leu Ser Pro Arg
 1860 1865 1870
 Gly Ser Arg Pro Ser Trp Gly Pro Thr Asp Pro Arg Arg Arg Ser Arg
 1875 1880 1885
 Asn Leu Gly Lys Val Ile Asp Thr Leu Thr Cys Gly Phe Ala Asp Leu
 1890 1895 1900
 Met Gly Tyr Ile Pro Leu Val Gly Ala Pro Leu Gly Gly Ala Ala Arg
 905 1910 1915 1920
 Ala